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CORTICO-HYPOTHALAMIC CONNEXIONS IN THE RABBIT

AN EXPERIMENTAL NEURO-ANATOMICAL STUDY

BY

PER OLOV LUNDBERG

UPPSALA 1960

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The English text was revised by Doctor Basil Finer

Uppsala 1960
Appelbergs Boktryckeri AB

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Introduction

In recent years increasing interest has been shown in the vegetative functions of the cerebral cortex. It is well-known that the hypothalamus is one of the most important parts of the brain with regard to vegetative regulation. From this fact one may assume that the cortico-hypothalamic nerve tracts are important links in the cortical regulation of vegetative functions. Therefore, the study of the cortico-hypothalamic connexions has aroused a great deal of interest.

Many authors have already tried to find nerve tracts from certain parts of the cortex to the hypothalamus. However, the results are often very divergent. In no previous study has the whole of the cortex been investigated for this purpose by one and same worker, and many parts of the cortex have not been studied at all. Most work has been done in man, monkeys, cats or rats. However, one animal especially well adapted to neuroendocrine and neuropharmacological work, the rabbit, has been very little studied in connexion with the present topic. For this reason, it has been chosen by the author.

In normal material it is very difficult to follow the nerve fibres from the different cortical areas as far as the hypothalamus. Instead, degeneration techniques have usually been adopted; that is to produce a destructive lesion in the cortex and to follow the appearence of degenerated nerve fibres in the hypothalamus. The simplest way of doing this, that of studying the atrophy of a tract macroscopically, was used in the earliest work on the direct cortico-hypothalamic connexions. Gudden (1881) observed that, following an extensive cortical ablation involving the hippocampus of the rabbit, the fornix on the operated side appeared after a time to be thinner.

Since then degeneration methods have evolved considerably. Several authors have used the Marchi technique. With this method it is possible to stain degenerated myelin sheaths with osmic acid. The main disadvantage of the method is that very fine degenerated nerve fibres remain unstained.

During the last 15 years two new methods have been developed, those of Glees (1946) and Nauta (1950, later modificated by Nauta & Gygax 1954). These two methods complement each other. The Glees method stains the whole of the neuron, both the axon, its arborizations and the terminal boutons, both normal and degenerated (Glees & Nauta 1955). It sometimes fails, however, in certain areas (for example the hypothalamus, Nauta & Gygax 1951). Cowan & Powell (1956) pointed out that artifacts ("pseudodegeneration") may sometimes be misinterpreted as degeneration. This is denied by Adey, Rudolph, Hine & Harritt (1958). It is always very laborious and often very difficult to follow the degenerated neurons in the mass of normal ones. In the Nauta & Gygax (1954) method, however, the staining of normal fibres is suppressed and thus the degenerated ones stand out more clearly. Unfortunately the terminal arborizations are not so well stained with this method. Glees & Nauta (1955) and Evans & Hamlyn (1956) therefore recommend using both techniques alternately.

The purpose of the present study was to investigate the direct connexions from the cerebral cortex of the rabbit to the hypothalamus making use of the staining methods of Nauta & Gygax (1954) and Glees (1946).

Material and Methods

For the present study 168 adult albino rabbits of both sexes weighing from about 2 to 4 kilograms were used. For reasons given below the results could be based on only 111 cases. It was difficult to obtain animals continuously during the time of the investigation (1955–59) and some of them became diseased. For this reason, it was necessary to take rabbits from a number of different breeders.

The lesions were made using two different methods. In 32 animals (R 73–R 223) smaller or larger parts of the cortex were destroyed with a knife or sucker, any possible bleeding being stopped with Spongostan or Gelfoam and the dura sutured. However, with this method it was not possible to reach all parts of the cortex and the lesions tended to be too large. Because of this, in 128 animals (R 225–R 368) lesions were made electrolytically by a direct current of about 3 mA for 30 to 90 seconds. Through a dental burr hole a unipolar electrode, insulated to the tip, was placed stereotaxically in the brain, and the indifferent, negative electrode was placed in the tongue. The stereotaxic co-ordinate system used was a further evolution of that used by Sawyer, Ewerett & Green (1954) for the rabbit diencephalon. It was found necessary to make as small a lesion as possible in the cortex. Larger lesions almost invariably resulted in damage to the blood vessels leading to huge subcortical infarcts.

Before the operations penicillin was administered to the animals, the operative technique aimed at being aseptic, and sulpha was applied topically. The lesions were made under Nembutal or Nembutal-chloralose anaesthesia. Afterwards the animals were observed daily for "physiological" effects of the lesions and if necessary (after the bigger operations) treated with antibiotics, Ringer's solution or glucose subcutaneously.

Between 4 and 17 days (normally about 7 days) after the operation the animals were anaesthetised again and the carotid system of the still living animal perfused with Ringer's solution followed by about 50 cc of 10 % formol. The brain and pituitary were dissected away and a post-mortem examination was made. If necessary the organs were studied microscopically. Unfortunately no less than 41 animals had a severe encephalitis. In all cases this was of the same type and caused lesions in many parts of the brain with secondary degeneration visible in the silver stains. These animals were excluded. The details will be described elsewhere (Sourander & Lundberg). Besides these animals another 16 had to be excluded from the material because of operative complications or disease not caused by the operation.

The brains were fixed in 10 % formol or formol-saline for at least three weeks. A central block including the diencephalon, the anterior part of the mesencephalon, the septal region, the area diagonalis and adjacent parts of the brain were dissected from the specimens. As most of the nerve bundles to the hypothalamus are arranged in the sagittal plane, the block was cut sagittally in series of frozen sections, 20 microns thick. From the beginning every 5th to every 10th section was stained according to Nauta & Gygax (1954). This method, however, sometimes gave precipitation artifacts in the hypothalamic region. A slight modification later in cases R 274–R 368 gave better results. The sections were soaked in 0.5 % phosphomolybdic acid overnight or at least for 5 hours, instead of the shorter time given by Nauta & Gygax. The time for the treatment with 0.05 % potassium permanganate was between 10 and 20 minutes. The unstained sections were saved and if necessary more of them were stained. Sometimes it was difficult to determine the exact place of termination of the degenerated nerve fibres with this method. In these cases suitable sections were stained with the Glees (1946) technique. To avoid overstaining in the hypothalamus the ammonia silver solution used in Glees original method had to be diluted.

Sometimes it was possible to get the whole lesion in the central block, in other cases the rest of the brain containing

the lesions was imbedded in paraffin, sectioned frontally in 10 microns thick sections, and stained with chromalunhematoxylin phloxine according to Gomori. To facilitate the determination of the topographic localization of the lesion and degeneration camera lucida drawings of the sections were made.

So that the author should be familiar with the normal anatomy, the brains from two animals were imbedded in paraffin, sectioned in series sagittally and frontally respectively, and stained by means of Palmgren's silver method (1948), the glia staining method according to Weil & Davenport, chromalunhematoxylin phloxine (Gomori) and the Nissl method.

CONTROLS

Droplike disintegration is a dependable criterion of axonal degeneration (Glees & Nauta 1955). However, as these authors and Cowan & Powell (1956) pointed out sporadic signs of degeneration are observed in "normal" brains, at least in the hypothalamus. Very often spindle-shaped swelling of normal axons can be observed, which should not be interpreted as degeneration. Incomplete impregnation and tangential sections of nerve fibres are also apt to be misinterpreted. The degenerative phenomena vary to some extent in different axons, depending partly on the thickness of the fibre. Besides there is a theoretical possibility that not all fibres become impregnated by the silver stain. It seemed necessary to become familiar with both the normal and the degenerative appearances of each nerve fibre bundle in the part of the brain concerned. To check this the author used two normal brains (R 149 and R 152) as controls, fixed and stained in the same way as the operated ones. Furthermore in other rabbits stereotaxically placed lesions were made in the fornix (R 322 and R 353), the stria terminalis (R 235, R 344), the stria medullaris (R 345 and R 346), the medial forebrain bundle (R 339), the pedunculus corporis mamillaris (R 234), the fasciculus ma-

millo-thalamicus (R 324 and R 345), the fasciculus mamillo-tegmentalis and other diencephalo-mesencephalic fibre tracts (R 289, R 290, R 355 and R 366) and in the nervous opticus (R 223, R 248 and R 336).

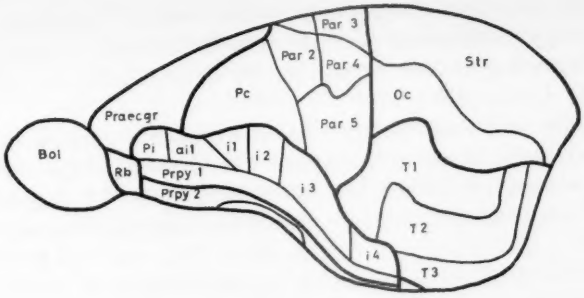
Because of technical difficulties, the Nauta & Gygax method sometimes fails. It therefore seemed best to cut the central block large enough to contain parts of the corpus callosum, the capsula interna and the cortico-thalamic tracts where the presence of degeneration could be checked in the nerve fibre tracts which were already well known.

Operations on the brain involve considerable risks. It is possible that the operation or the anaesthesia cause non-specific damage to the brain and subsequent axonal degeneration. Of course cerebral hypoxia was avoided as far as possible. The anaesthesia was as short and superficial as possible. The electrolytic operations took a very short time (about 15 minutes) and about one hour and a half after the beginning of the anaesthesia the animals were awake. The other operations took a somewhat longer time. Nembutal anaesthesia produces a fall in the blood pressure. This can be diminished by using a combination of Nembutal and chloralose (Söderberg, personal communication). Most of the operations seemed to affect the animals very little. To study the possibility of non-specific damage four controls were used. Two animals (R 165 10d and R 168 9d) underwent a large craniotomy and two others cervical sympathectomy (R 98 17d and R 200 8d). Except for the specific lesion the whole procedure was carried out in the same way as with the subjects. In none of these four controls were any degenerated nerve fibres found in the hypothalamus.

Nomenclature

The extensive study of the cytoarchitectonic areas in the cerebral cortex of the rabbit by M. Rose (1931) still seems to hold good and his maps have been used as a basis in the present study. However, his nomenclature differs somewhat in detail from those more commonly used. Zunino (1909) has made a comprehensive study of the myeloarchitecture in the rabbit's cortex. His main subdivisions agree with those of M. Rose. Zunino has given a transposition of his nomenclature into that of Brodmann commonly used both for the rabbit and for the higher animals (review see Rose 1931 and Kappers, Huber & Crosby 1936). Winkler & Potter (1911) have given some information about the cortex in their atlas of the rabbit brain. Neurophysiological work by Woolsey et al (reviewed

Figures 1–4: A map of the rabbit's cerebral cortex redrawn and slightly modified from M. Rose (1931). The abbreviations are strictly according to Rose. ai 1–3: area insularis agranularis. Bol: bulbus olfactorius. Diag: regio diagonalis. e 1–9: regio entorhinalis (nine areas). FD: fascia dentata. i 1–4: regio insularis granularis (four areas). IRa α: area infraradiata ventralis anterior. IRb α: area infraradiata intermedia anterior. IRc α: area infraradiata dorsalis anterior. IRabc β: area infraradiata posterior. Oc: area occipitalis. Pam: regio periamygdalaris. Par 1–5: regio parietalis (five areas). Parsub: area parasubicularis. Pc: regio postcentralis. Pi: area preinsularis. Praecag: regio precentralis agranularis. Praecgr: regio precentralis granularis. Prpy 1: area prepyriformis lateralis. Prpy 2: area prepyriformis medialis. Prpy 3: area prepyriformis intermedia. Prsub 1: area presubicularis dorsalis. Prsub 2: area presubicularis ventralis. Pstr: area peristriata. Rb: regio retrobulbaris. Rsg α: area retrosplenialis granularis ventralis. Rsg β: area retrosplenialis granularis dorsalis. Rsg γ: area retrosplenialis granularis infima. Spell: septum pellucidum. Str: area striata. Sub: subiculum. T 1–3: regio temporalis (three areas). Tol: tuberculum olfactorium. tt: taenia tecta.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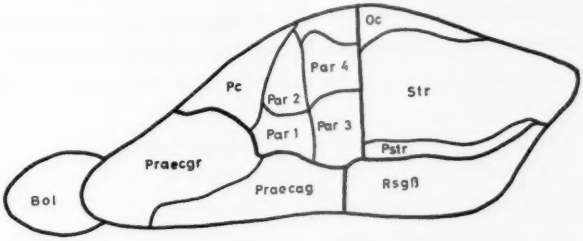
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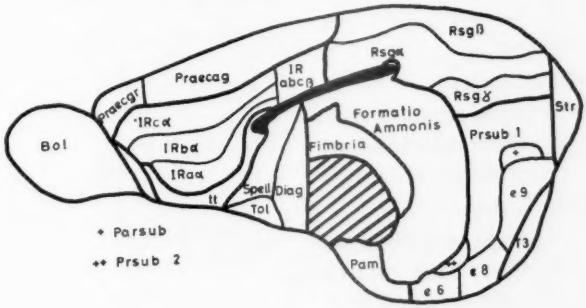
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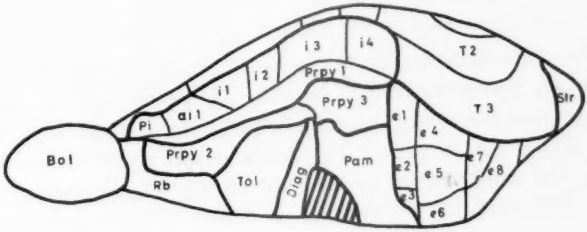
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4

by Woolsey 1958) have given further results concerning the homology of different cortical areas in different animals. At the beginning of each section details of nomenclature will be briefly discussed.

In the following, the material is grouped according to the cortical areas in which the lesions were placed and the cortical subdivisions are named according to M. Rose. The abbreviations are in strict accordance with his, and explanations are found in connexion with figures 1 to 4. The main subdivisions of the cerebral cortex in rabbits are according to M. Rose:

I. Holocortex septemstratificatus (by others called neocortex). For practical reasons this will be divided into a frontal part, a parietal part, an occipital part and a temporal part.

II. Holocortex quinquestratificatus.
   a. regio orbitalis
   b. regio infraradiata sive limbica anterior
   c. regio retrosplenialis granularis

III. Holocortex bistratificatus.
   a. regio retrobularis
   b. formatio Ammonis

IV. Bicortex.

V. Schizocortex.
   a. regio presubicularis
   b. regio entorhinalis
   c. regio perirhinalis

VI. Semicortex.
   a. regio prepyriformis
   b. tuberculum olfactorium
   c. regio diagonalis
   d. septum pellucidum
   e. regio periamygdalaris

The nomenclature of the subcortical regions in the rabbit is much more confusing. Winkler & Potter (1911) made a comprehensive study in their atlas with frontal sections of the whole rabbit brain. The non-cortical parts of the telencephalon were studied in 1936 by Young. The pretectal region was described by Kuhlenbeck & Miller (1942). A stereotaxic

atlas of the rabbit diencephalon was made by Sawyer, Everett and Green (1954). There are at least four extensive studies devoted to the hypothalamic cytoarchitecture in the rabbit: Grünthal (1931), Miura (1933), M. Rose (1935) and Wahren (1957). However, they subdivide the hypothalamus in different ways and their opinions are difficult to reconcile. The present results will add some arguments to the dispute about hypothalamic nuclei. Details about the nomenclature will be discussed later.

It should be noticed, that the definition of the hypothalamic region is that of Kappers, Huber & Crosby (1936). Thus, the entopeduncular nuclear group, the zona incerta, the fields of Forel, the subthalamic nucleus, or the globus pallidus are not included in the hypothalamus.

Results

In the following a detailed description and a diagramatic sketch of the lesions (figures 5–12, 15–20) is given for all rabbits in the different groups. It should be noticed that sometimes the lesions exceeded the boundaries of the actual cortical region and if there was significant damage to the adjacent area the case was also described in relation to the latter. If there was no significant degeneration in the hypothalamic region no further details concerning degeneration in the internal capsule, the thalamus etc. are given. The degeneration described in the following was always ipsilateral to the lesion unless the reverse is pointed out. The number given in brackets after each animal indicates the number of days between operation and death. The discussion of the previous investigations concerning the direct cortico-hypothalamic connexions follows under the description of each group.

I. Holocortex Septemstratificatus

THE FRONTAL PART

Cortical subdivisions:

This was subdivided by Rose into the regio precentralis agranularis (Praecag) corresponding to area 4 (Brodmann 1909) and the regio precentralis granularis (Praecgr) consisting of the area frontalis (area 6) and the area parorbitalis (area 8) according to Winkler & Potter. The most rostral tip of the frontal cortex was called the orbitofrontal region (area 12) by J. Rose & Woolsey (1949). Neurophysiological work by Woolsey (1958) has shown that the supplementary motor area (II) is localized on the medial surface of the regio precentralis agranularis and that the motor area I is situated in the region of the frontal cortex corresponding to the lateral part of the regio precentralis agranularis and in the regio precentralis granularis.

Present results:

Thirteen cases showed significant damage to the frontal cortex (figures 5–10). In eleven of them there were no degenerated nerve fibres in the hypothalamus.

R 114 (10d): A relatively small lesion in the lateral part of Praecag going deep into the radiatio corporis callosi.

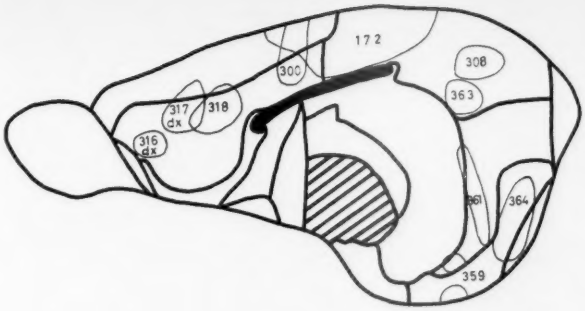
R 155 (8d): A large lesion involving the anterior part of Praecag and part of Praecgr and in its deepest part just reaching the white substance.

R 204 (7d): Most of this relatively superficial lesion lay in the postcentral region (Pc), part of it, however, going into the layers I and II of Praecgr.

R 226 (7d): This lesion was localized in Praecag, on its medial surface going to the boundaries of the regio infraradiata. The lesion involved all cortical layers.

R 249 (6d): The lesion lay in the anterior part of Praecgr

Figures 5–12: On these maps the approximate position of the cortical lesions are seen in all the cases except in those rabbits where the destruction lay in Ammon's formation. Only the main cortical divisions are drawn in these maps.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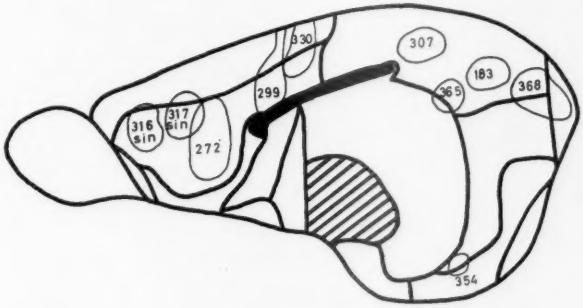
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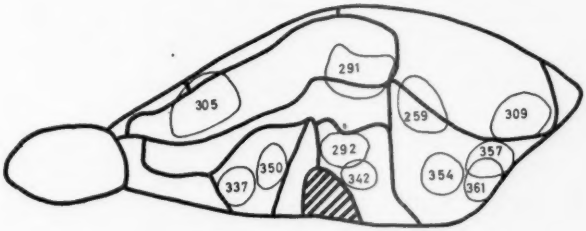
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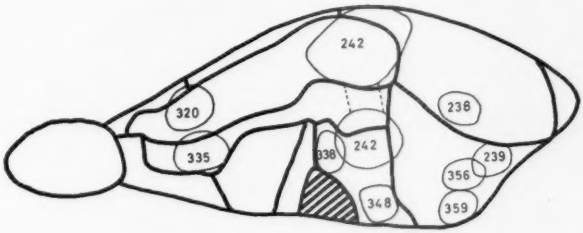
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12

corresponding to the whole of area 8 and adjacent parts of area 6 and 12 and went into the insular cortex. It involved all cortical layers.

R 257 (7d): This relatively small lesion involved the anterior part of Praecgr corresponding to part of area 12 and the anterior part of area 6. Only most deeply were all the cortical layers damaged.

R 258 (7d): This lesion was localized to the tip of Praecgr corresponding to the orbitofrontal region, most of which was destroyed.

R 294 (12d): A relatively superficial lesion at the boundary of Praecag and Praecgr. Only layers I to V were destroyed.

R 300 (11d): This lesion destroyed all the cortical layers of Praecag and went into the regio infraradiata.

R 329 (6d): This lesion lay in the anterior part of Praecag and in its deepest part just reached the white substance.

R 330 (7d): The lesion involved the posterior part of the medial surface of Praecag, destroying all cortical layers, and went into the regio infraradiata.

In the following two brains degenerated nerve bundles were seen in the hypothalamus.

R 315 (7d): The main lesion was in the insular cortex and in the prepyriform cortex near the olfactory tract but the electrode on its way down had damaged a great deal of Praecgr. In this brain there was degeneration in the hypothalamus seen in the medial forebrain bundle which is described later.

R 321 (7d): As well as a considerable lesion in Praecgr and the postcentral cortex (Pc) there was a great deal of damage to the white matter (the radiatio corporis callosi, the capsula interna and externa) and probably also to the nucleus caudatus. In this case some degenerated nerve fibres were seen in the preoptic region, in the ventromedial hypothalamic nucleus and in the subthalamic nucleus.

The first eleven of these cases include almost all of the frontal parts of the neocortex and no degeneration was found in the hypothalamic area. The occurrence of degeneration in the hypothalamus in the last two cases can clearly be explained by damage to other brain structures.

Previous investigations:

Connexions between the frontal lobe and the hypothalamus have been described earlier by several authors, using other methods and animals. Strychnine neuronography as described by Dusser de Barenne and McCulloch was used in cats by Murphy & Gellhorn (1945) and Niemer & Jimenes-Castellanos (1950), and in monkeys by Ward & McCulloch (1947) and Peterson & Bickers (1952). This method, however, has some well-known disadvantages. Frankenhaeuser (1951) among others showed that strychninisation of some parts of the brain does not elicit strychnine spikes. Wall & Horwitz (1951) presented evidence that "strychnine influences the excitability of axons at a distance by a probable electrotonic effect from increased internuncial activity" and that synchronized volleys produced by strychnine may cross a synapse. A direct (anatomical) connexion is thus not proved by the presence of strychnine spikes and the existence of a nerve tract is not excluded by such spikes.

Many authors have used various degeneration techniques. After lesions in different parts of the frontal lobe disintegration of the myelin sheaths has been studied with the aid of Marchi's stain or the occurrence of degenerated boutons has been investigated in Glees stained preparations. Others have used the Nauta & Gygax method or Gibson's modification of the Rio-Hortega technique.

Meyer (1949, Glees method), Beck et al (1951, Glees method), Kanki & Ban (1952, Marchi method) and Smythies et al (1957, Gibson method) worked on lobotomized human patients. In these cases the operations involved an extensive damage to both white and grey substance in the subcortex making it very difficult to draw any conclusions about the connexions between the frontal *cortex* and the hypothalamus.

Milliser (1932, rat) and Levin (1936, monkey) both using the Marchi technique, failed to show any direct connexions between the frontal cortex and the hypothalamus. The results of other authors working with degeneration studies on animals are very divergent and their series were very small. Mettler described (1935 b and 1947, Marchi method) nerve fibres in the

monkey from area 6 to the posterior hypothalamic area, LeGros Clark & Meyer (1950, Glees method) working on the same animal reported connexions from the same cortical area to the ventromedial hypothalamic nuclei on both sides. Adey et al (1958, Nauta and Glees methods) noticed degeneration in the ventromedial and dorsomedial nuclei in one monkey after ablation of areas 8B and 9. After lesions in areas 6 and 8 in cats Kurotsu et al (1953) found Marchi granules in the periventricular region of the hypothalamus. Auer (1956, Nauta & Gygax method), however, found degenerated nerve fibres in the medial forebrain bundle. It can be seen that the results of earlier investigations seem to be very controversial.

No studies have previously been made in the rabbit. It should be remembered that the rabbit is more primitive than the monkey and the cat, and that the frontal cortex has undergone a tremendous evolution in the higher animals (see e.g. Woolsey 1958). It is possible that fronto-hypothalamic connexions have developed there.

THE PARIETAL PART

Cortical subdivisions:

This was subdivided by M. Rose into the regio postcentralis (Pc) corresponding to areas 1–3 and the regio parietalis corresponding to areas 5 and 7. Rose further divided the regio parietalis into five areas (Par 1–5). Neurophysiological work carried out on rabbits by Adey & Kerr (1954) and Woolsey & Wang (1945) have shown that the somatic sensory area I is localized to Pc and Par 1–4 and the somatic sensory area II to Par 5.

Present results:

In the present study there were ten cases with significant damage to the parietal part of the neocortex (figures 5–8). In the following seven cases there was no degeneration in the hypothalamic region.

R 111 (10d): A relatively small and superficial lesion in Par 3 and Par 4 involving the cortical layers I–III.

R 204 (7d): There was damage of the anterior postcentral region (Pc) where the cortical layers I–IV were destroyed.

R 232 (4d): This lesion involved all cortical layers in Par 4 and Par 5.

R 237 (4d): An extensive and deep lesion involving the posterior part of the postcentral region (Pc), most of Par 2 and 5 and extending into the insular region.

R 255 (7d): This lesion involved all cortical layers in most of Par 1 and Par 2.

R 306 (10d): The main lesion was found in the insular cortex. On its way the electrode had produced considerable damage to the postcentral region.

R 328 (6d): A distinct lesion in Par 3 involving all the cortical layers.

In three cases (R 73 5d, R 112 10d and R 327 4d) there was considerable destruction of the parietal cortex (Par 1 and Par 3 respectively) but the lesions continued into the hippocampus. In these cases degenerated nerve fibres in the fornix system were seen in the hypothalamus.

Previous investigations:

There is very little information in the literature about possible parieto-hypothalamic connexions. Mettler (1935 c) briefly mentioned the occurrence of degenerated myelin sheaths in the lateral hypothalamic area of a few monkeys after lesions in the parietal lobe. The lateral hypothalamic area is situated just beneath the internal capsule where degenerated nerve fibres passed by in all the author's cases. However, no signs of deviation into the hypothalamus proper or termination in the lateral hypothalamic area were found in this study.

THE OCCIPITAL PART

Cortical subdivisions:

This was divided by Rose into the area striata (area 17), the area occipitalis (area 18) and the very thin area peristriata.

The area striata corresponds to visual area I and the area occipitalis to visual area II (Thompson, Woolsey & Talbot 1950).

Present results:

In the present study there were eleven specimens with significant lesions in the occipital part of the cortex (figures 5–8). In eight of them there were no degenerated nerve fibres in the hypothalamic region.

R 132 (15d): A relatively small lesion in the area peristriata. Only the layers I to V were destroyed.

R 254 (5d): Even this lesion was very small. It was localized to the area striata and involved layers I to IV.

R 256 (7d): A somewhat bigger lesion in the area striata involving all layers.

R 264 (4d): This lesion lay in the area peristriata and the area striata and just reached the white matter.

R 296 (12d): A very superficial lesion (only the layers I–III) in the area striata.

R 303 (10d): A big lesion involving the layers I–IV(V) in the area striata.

R 310 (8d): A very big lesion involving all layers of the area occipitalis and proceeding into the temporal neocortex.

R 326 (7d): Two very small and superficial lesions in the area striata.

In the following three cases there was a scanty degeneration in the fornix going to the mamillary body.

R 112 (10d): A relatively large lesion involving the anterior part of the areas striata and peristriata going into the parietal region. In its deepest place the lesion went through the radiatio corporis callosi and the tapetum, slightly damaging the superficial layer of the alveus.

R 166 (9d): A big lesion destroying part of the area occipitalis and part of the temporal neocortex. The lesion went through the lateral ventricle and damaged the alveus.

R 325 (6d): This lesion in the area striata went into the radiatio corporis callosi, damaging the tapetum and probably producing destruction in the alvear path.

It is well known (and it is studied more fully later in this work) that the alveus sends nerve fibres through the fornix. It is therefore most probable that the fornix degeneration in the last three cases is not caused by the lesion in the occipital cortex itself but by the alvear damage. It has been very difficult to produce lesions in the occipital cortex without damaging Ammon's formation. This is why most of the lesions described above are so superficial.

Previous investigations:

In his paper on the corticofugal connexions from the occipital region of the monkey, Mettler (1935 a) did not mention any fibres to the hypothalamus. Apart from this paper, no previous studies have been made.

THE TEMPORAL PART

Cortical subdivisions:

Rose subdivides this into three areas, T 1–3. The first (T 1) roughly corresponds to area 22 (Brodmann) or the auditory cortex I of Woolsey (1958), T 2 to area 20 and 21 or the auditory cortex II and T 3 to the area ectorhinalis (Zunino 1909) or area 36 according to Brodmann.

Present results:

In the present material there are nine cases with sufficiently extensive damage to the temporal neocortex (figures 7–8 and 11–12). In the following five there were no degenerated nerve fibres in the hypothalamus.

R 237 (4d): A large lesion going from the parietal cortex through the anterior part of the temporal neocortex to the insular cortex. Partly all cortical layers were involved.

R 240 (3d): A relatively large lesion starting in the inferior part of the area occipitalis and going through the anterior part of the temporal cortex involving all cortical layers in part of T 1 and T 2.

R 259 (7d): This lesion involved the cortical layers IV–VII in a part of T 3 and proceeded into the entorhinal cortex.

R 310 (8d): In this case the lesion started in the area occipitalis and went through all temporal areas involving the layers I–V(VI).

R 311 (8d): This lesion involved the anterior part of T 3 and part of T 2. Only cortical layers I–V were damaged.

In the following four cases there were some degenerated nerve fibres in the hypothalamus or the preoptic region.

R 166 (9d): This lesion involved a large part of T 1–2 and the inferior part of the occipital area. However, the lesion extended into the lateral ventricle and the superficial alvear path was damaged. In the hypothalamus there was scanty degeneration in the fornix and mamillary body.

R 238 (6d): In this brain there was a lesion of all the cortical layers of T 3 and the area perirhinalis. The lesion reached just to the alvear path. The case was difficult to interpret because of precipitation artifacts but there seemed at least to be some degenerated nerve fibres in the fornix.

R 309 (8d): Besides a considerable lesion in T 3 and the area perirhinalis there was a significant damage to area h 2 in the hippocampus. There was severe degeneration in the fornix system, which is described later.

Thus, in these three cases the hypothalamic degeneration seemed to be explained by damage to Ammon's formation.

R 242 (5d): This very large lesion also included damage to the anterior part of T 1 and 2. In the preoptic region and probably also in the lateral hypothalamus there were a few degenerated nerve fibres. This is discussed later, but it seems probable that this degeneration came from the prepyriform cortex.

Previous investigations:

There have been some previous studies of temporo-hypothalamic connexions. Strychinisation of the auditory cortex produced "firing" of the hypothalamus (Murphy & Gellhorn 1945, Niemer & Jimenez-Castellanos 1950). The result of this

"physiological neuronography" is, however, difficult to estimate. Adey & Meyer (1952 a) with Glees method studied the monkey's hypothalamus after temporal lobe ablation in two cases. One animal with a small lesion in area 38 had bilateral, terminal degeneration in the caudal part of the ventromedial and arcuate nuclei. There was no degeneration in the stria terminalis. In the other animal with a lesion in area 22 no degenerated nerve fibres were found in the hypothalamus. Whitlock & Nauta (1956) worked with the Nauta & Gygax technique. In their description of eight monkeys with lesions in most parts of the temporal neocortex they did not mention any degeneration in the hypothalamus.

CONCLUSIONS

Thirty-eight rabbits with lesions in the neocortex were used. No evidence was found of any direct connexions from the rabbit's neocortex to the hypothalamus.

II. Holocortex Quinquestratificatus

A. REGIO ORBITALIS

This is a very small cortical region just underneath the frontal tip. In cases R 257 and R 258 described in the section on the frontal cortex, there were lesions in the regio orbitalis. No degeneration was found in the hypothalamus of these cases.

B. REGIO INFRARADIATA SIVE LIMBICA ANTERIOR

Cortical subdivisions:

The subdivisions of this region according to the different authors (M. Rose, J. Rose & Woolsey, Zunino and Brodmann) were as follows:
Area infraradiata ventralis anterior (IRa α) ~ infralimbic area ~ area subgenualis ~ area 25.
Area infraradiata intermedia anterior (IRb α) ~ part of the anterior limbic region ~ area prelimbica ~ area 32.
Area infraradiata dorsalis anterior (IRc α) ~ part of the anterior limbic region ~ area limbica anterior ~ area 24.
Area infraradiata posterior (ventralis IRa β, intermedia IRb β dorsalis IRc β) ~ part of the anterior limbic region ~ area limbica media ~ area 23.

Present results:

Of the seven cases with significant damage to the regio infraradiata (figures 9–10) there were five brains without any degeneration in the hypothalamus.

R 300 (11d): This lesion began in the precentral cortex and involved all cortical layers in IRabc β.

R 316 (7d): On the left side there was slight damage to the

precentral cortex and a considerable lesion in IRc α and IRb α involving all layers. On the right side there was a superficial lesion in IRb α.

R 317 (7d): On the left side there was destruction in IRc α going into the superior part of the white matter. On the right side the lesion began in the precentral cortex and involved only the layers I–V in IRc α.

R 318 (7d): Besides a small damaged area in the precentral cortex there was a lesion in IRc α and IRb α including all cortical layers in the former area.

R 330 (7d): The lesion lay at the boundary between the precentral cortex and IRabc β and went a little way into the white matter.

In the two other cases there was degeneration in the hypothalamus.

R 272 (7d): The lesion began in the precentral cortex and went through IRc α, IRb α and IRa α damaging also the caput of the caudate nucleus.

R 299 (11d): This lesion involved IRabc β on both sides and also the superior aspect of the corpus callosum with the taenia tecta and the subiculum. There were a few degenerated nerve fibres in the fornix and mamillary body.

Previous investigations:

There have not been any previous anatomical studies of the possible connexions between the regio infraradiata and the hypothalamus. However, after local application of strychnine to the cat's limbic cortex both Murphy & Gellhorn (1945) and Niemer & Jimenez-Castellanos (1950) observed "firing" of the hypothalamus. The disadvantages of this method have been mentioned above. Jasper et al (1952) demonstrated the conduction of after-discharges to the mamillary region following stimulation of the anterior cingulate gyrus in the monkey. However, they stated that "the presence of strong synaptic relays is not ruled out by this method" (cf page 158). Thus, at present there is no proof of a direct tract from the regio infraradiata to the hypothalamus.

C. REGIO RETROSPLENALIS GRANULARIS

Cortical subdivisions:

This part of the cortex was called the area retrolimbica by Zunino and area 29 by Brodmann. M. Rose divided it into a ventral part (Rsg α), a pars infima (Rsg γ) and a dorsal part (Rsg β). The first two were called the retrosplenial area and the last one the cingular (or cingulate) area by J. Rose & Woolsey.

Present results:

There were 12 cases with significant damage to the regio retrosplenialis (figures 5–6 and 9–10).

R 127 (15d): There was extensive damage to the greater part of (Rsg β) but the lesion went through the white matter and there was a slight injury to the alvear path.

R 171 (9d): The lesion involved all cortical layers of the left Rsg β but also extended into Praecag and the right Rsg β. There was the suspicion of an injury to Ammon's formation.

R 172 (9d): The lesion included a large part of Rsg β on both sides. However, it also extended into the corpus callosum with damage to the fornix longus and the taenia tecta. The lesion also involved a part of Praecag and of IRabc β.

R 182 (8d): The lesion involved all cortical layers of the posterior part of Rsg β and the adjacent area striata. Owing to vascular damage there was an infarct in the colliculus superior.

R 183 (8d): There was a relatively small penetrating lesion going from Rsg β to Rsg α. There was also a vascular infarct in the colliculus superior in this preparation.

R 301 (11d): This lesion involved all cortical layers of Rsg β at the boundary with Praecag. It extended into the cingulum and the tapetum. A few superficial fibres in the alvear path seemed to be degenerated.

R 307 (10d): This lesion involved a small part of Rsg β and a somewhat larger part of Rsg α. It involved all cortical layers.

R 308 (10d): This lesion was rather small and lay at the boundary between Rsg β and Rsg α. It also proceeded a little way into the superior collicle.

R 323 (7d): In this brain the lesion lay in the anterior part of Rsg β and extended through the corpus callosum and the fornix longus to the taenia tecta.

R 363 (5d): The lesion went through the area striata and Rsg α and damaged the lateral aspect of the mesencephalon.

R 365 (6d): Here there was a distinct lesion in the subiculum and in Rsg γ near it.

R 368 (6d): The lesion lay in the posterior tip of the brain and involved part of the area striata and part of Rsg α and Rsg γ and the area presubicularis.

In all of these 12 cases there was damage to all cortical layers in the regio retrosplenialis.

In some of these cases (R 182, R 183, R 308 and R 363) there was also a lesion in the mesencephalon. The degenerated nerve fibres from these lesions were easy to identify. They were not going to the hypothalamus and are not described in the present paper.

In all the cases (R 182, R 183, R 307, R 308, R 363, R 368) where the cortical lesion was confined to the regio retrosplenialis and where there was no suspicion of injury to Ammon's formation or any efferent tracts from it a slight but distinct degeneration in the fornix longus was found. Details are given for a typical case, R 363 (figure 13). The degenerated nerve fibres entered the diencephalic region in the medially situated fornix longus and proceeded in the descending ipsilateral hypothalamic fornix to the mamillary body. In the region of the septum part of the nerve fibres left the tract and entered the medial septal area. There was a distinct terminal degeneration around the big nerve cells just in front of the medial column of the fornix. No significant nerve fibres left the region of the medial septal nuclei. In the mamillary body at least preterminal degenerated nerve fibres were found in the lateral part. The distribution of the degeneration corresponded to the nucleus mamillaris lateralis and intermedius. However, part of the degenerated nerve fibres continued into the supra-

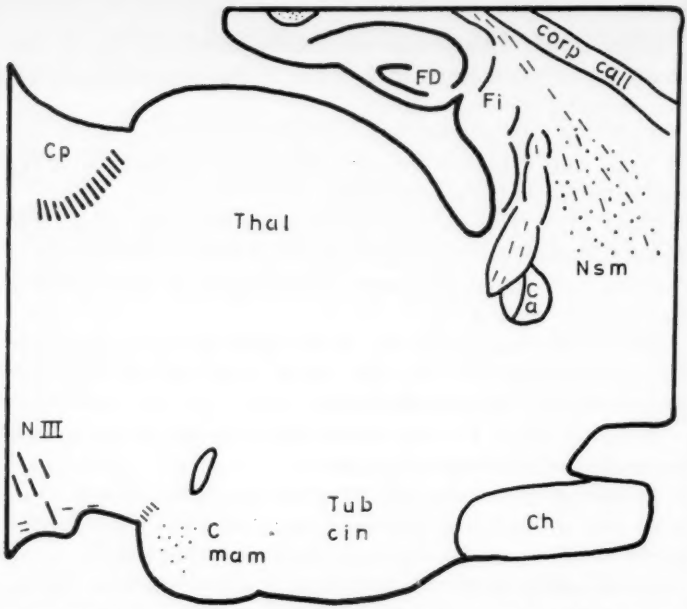


Figure 13: A sagittal section of the diencephalon and septal region of case R 363 about 0.5 mm lateral to the median plane ipsilateral to the lesion. Figures 13 and 21–26 are redrawings from camera lucida drawings of representative Nauta & Gygax stained sections from the different cases. Only some of the main structures are shown to guide the reader. The fine streaks indicate passing degenerated nerve fibres, the fine dots indicate terminal degeneration. It is to be noticed that the degenerated nerve fibres drawn are only from that particular section. Abbreviations: Aq: aqueductus mesencephali. Ca: commissura anterior. Caps mam: capsula corporis mamillaris. Ch: chiasma. Corp call: corpus callosum. Cp: commissura posterior. Dsm: decussatio supramamillaris. Fi: fimbria hippocampi. FM: fasciculus retroflexus Meynert. Fmt: fasciculus mamillo-tegmentalis. Fmth: fasciculus mamillo-thalamicus. Fo: fornix. Hab: nucleus habenulae. Mes: mesencephalon. MFB: medial forebrain bundle. N III: nervus oculomotorius. N caud: nucleus caudatus. Nmb: nucleus mamillaris basalis. Nml: nucleus mamillaris lateralis. Nmm: nucleus mamillaris medialis. Np: nuclei pontis. Npf: nucleus perifornicalis. Nr: nucleus ruber. Nsl: nuclei septi laterales. Nsm: nuclei septi mediales. Nsum: nucleus supramedialis thalami. Pcm: pedunculus corporis mamillaris. Po: preoptic region. Psv: psalterium ventrale. Pthi: pedunculus thalamicus inferior. Sm: stria medullaris. St: stria terminalis. Sth: nucleus subthalamicus. Thal: thalamus. Tub cin: tuber cinereum. Ventr: the brain ventricle system.

mamillary decussation and in a tract situated medially to the ipsilateral mamillary peduncle.

In the other cases there was damage either to the fornix longus itself (R 172 and R 323) or to Ammon's formation (R 127, R 171, R 301 and R 365). Here were found not only the degeneration mentioned above but also more degeneration described later under the section of Ammon's formation.

Previous investigations:

The connexions of the retrosplenial region in rabbits were studied by Cragg & Hamlyn (1959). In three cases with small lesions in the cingulate or retrospenial areas they found degenerated nerve fibres in the fornix longus.

CONCLUSIONS

Twenty-one rabbits with lesions in the holocortex quinquestratificatus were used. No indication of any direct connexions from the regio orbitalis and infraradiata to the hypothalamus was found. Evidence was given of a nerve fibre tract coming from the regio retrosplenialis via the fornix longus and the descending column of the fornix. Many nerve fibres terminated in the mamillary body, while others proceeded into the mesencephalon.

III. Holocortex Bistratificatus

A. REGIO RETROBULBARIS

This region corresponds to the nucleus olfactorius anterior (Young 1936). The nucleus lies partly in the olfactory bulb and many authors do not consider it as a part of the cortex. It has not been studied in the present work.

B. AMMON'S FORMATION

Ammon's formation, the hippocampus, or the archicortex is divided by most authors into the cornu Ammonis, the fascia dentata, the subiculum and the taenia tecta. The cornu Ammonis or cornu hippocampi is further subdivided by M. Rose into five fields (h 1–h 5).

Since the time of the old anatomists it has been known that the fornix provides a connexion between Ammon's formation and the hypothalamus. In rabbits according to von Koelliker (1894) besides the main fornix, starting on both sides from the fimbria hippocampi, there are nerve fibres which penetrate the corpus callosum from the deepest layer of the cingulate gyrus and also from the superior part of the hippocampus. This tract, called the fornix longus or dorsalis, thus goes in the centre of the corpus callosum (Cajal 1893) and enters the main fornix medially in the posterior part of the septum (figure 14).

The intentions in the present study have been to find out whether there are fornix fibres to the hypothalamus from all parts of the hippocampus and to study the place of termination in the hypothalamus. Besides some information about the termination of the non-hypothalamic fornix fibres was obtained. As a complement to the Nauta studies the Glees pre-

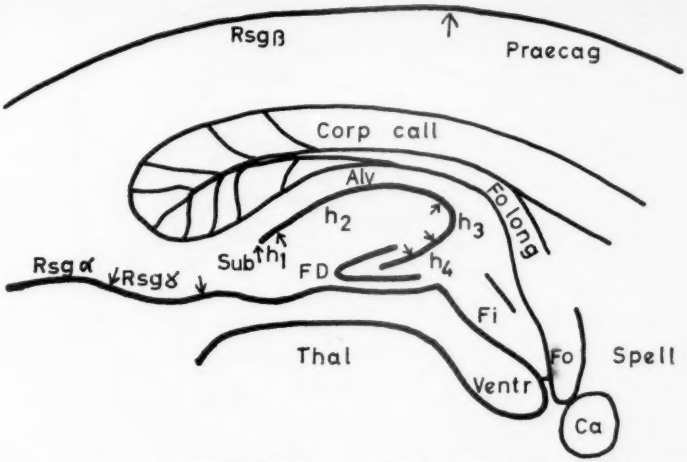


Figure 14: A diagrammatic sketch of Ammon's formation and the fornix system in the rabbit. The section is sagittal and a few mm lateral to the median plane. Abbreviations: Alv: alveus. C a: commissura anterior. Corp call: corpus callosum. Fi: fimbria hippocampi. Fo: the main fornix column. Fo long: fornix longus. h 1–5: the fields of the cornu hippocampi. Thal: thalamus. Ventr: the brain ventricle system. The arrows indicate the boundary between two cortical areas.

parations were valuable. The author has tried to confine the lesions strictly to one certain part of the hippocampus. This has, however, only been possible to some extent.

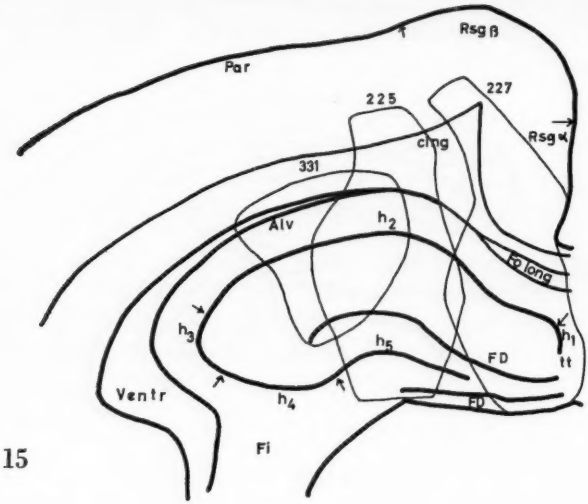
The field h 1:

The field h 1 just on the border to the subiculum is very small and in the cases where it was injured (R 225, R 227 and R 239), there was also extensive damage to other parts of the hippocampus (figures 15, 18 and 20).

The field h 2:

There were two cases where the hippocampal lesions were confined to the field h 2 (figures 18 and 19).

R 309 (8d): In this case there was longitudinal damage to



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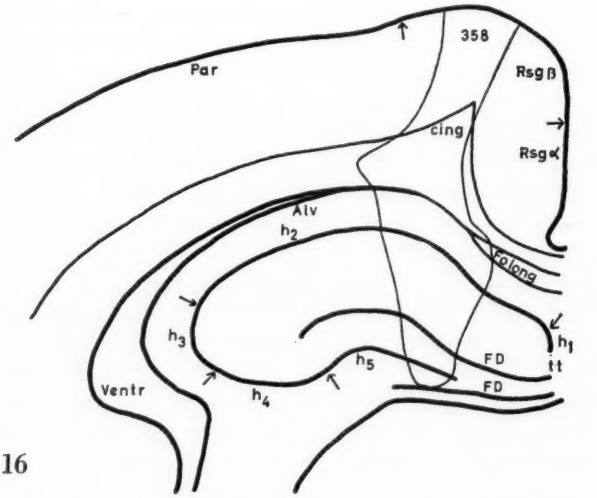

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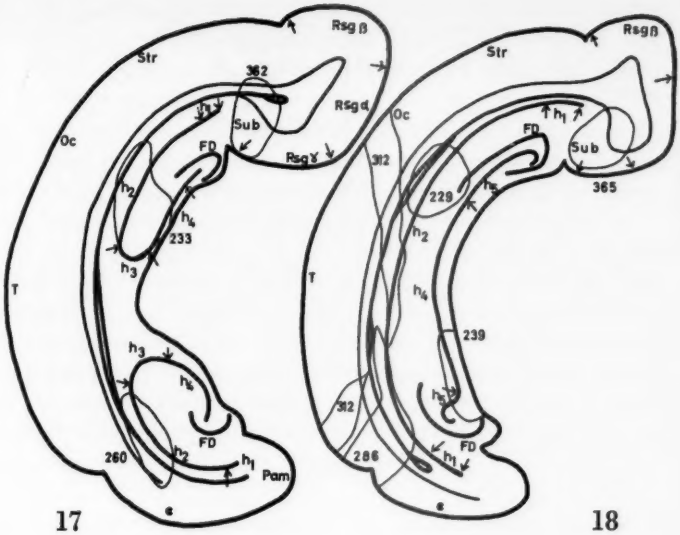
Figures 15–20: A series of frontal sections through Ammon's formation made after camera lucida drawings. One significant section from each of the different cases with lesions in the Ammon's formation is projected



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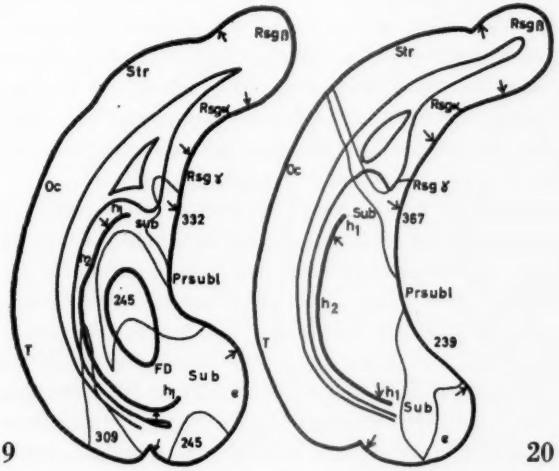

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on to these drawings and the approximate outlines of the lesion is copied on to a suitable drawing. For abbrevations, see legend under figs. 1 and 14.

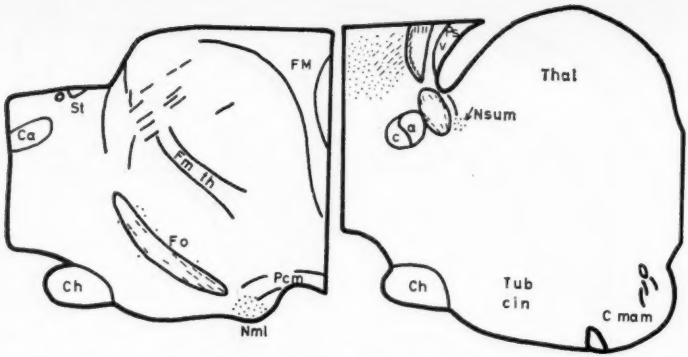

Figure 21: Two sagittal sections of the diencephalon of case R 312. The left one is about 1.5 mm lateral to the median plane and the right one is just lateral to it, both on the side ipsilateral to the lesion. For abbreviations, see legend under fig. 13.

the alveus, the stratum oriens, and the stratum pyramidale of the lateral part of the field h 2. The lesion extended into the temporal neocortex.

R 312 (8d): Here there was more extensive damage to the same part of the field. The layers from the alveus to the stratum radiatum were completely destroyed and in the stratum lacunosum and moleculare there was some reaction. The lesion began in the occipital region and proceeded a small distance into the temporal neocortex.

There were no significant discrepancies between the findings of degenerated nerve fibres in the two cases. The degeneration in the last case (R 312) was more abundant and is described in detail (figure 21). There were some degenerated nerve fibres in the psalterium ventrale. The nerve fibres ran in the fimbria and went through the septal region via the anterior part of the fornix bundle. Here many nerve fibres diverged from the fornix into the septum. Terminal degeneration at the big nerve cells was found in the medial septal nuclei. Just behind the anterior commissure a few nerve fibres entered the stria medullaris. Their place of termination was not found. Others went into the anterior thalamus where they seemed

to terminate in the nucleus supramedialis (according to the nomenclature of M. Rose). In the hypothalamus only very few nerve fibres left the fornix on their way to the mamillary body. They were not found beyond the area of the nucleus perifornicalis. All other nerve fibres terminated in the lateral mamillary nucleus and none was found in the mesencephalon. Besides the fornix fibres described no degenerated nerve fibres were found in the hypothalamic region of the two cases.

In many other cases (R 225, R 227, R 229, R 233, R 286, R 331, R 358) with hippocampal lesions there was also damage to the field h 2 (figures 15–18). Here all the degeneration described for case R 312 was found in the hypothalamus. In case R 260 (7d) there was both damage to the field h 2 of the hippocampus and a slight injury to the prepiriform semicortex and in the hypothalamus some degenerated nerve fibres were seen in the medial forebrain bundle.

The field h 3:

In rabbit R 286 (7d) in addition to a lesion in the posterolateral part of the field h 2 there was also a lesion in the field h 3. The injury in both fields was confined to the alveus, the stratum oriens and the stratum pyramidale. The lesion proceeded into the temporal cortex. In this case degeneration was found in the psalterium ventrale, the fimbria, the fornix, and the stria medullaris and terminations in the medial septal nuclei, the nucleus supramedialis and perifornicalis (figure 22). This is the same as in cases R 309 and R 312. However, in the mamillary body there not only was terminal degeneration in the lateral mamillary nucleus but also in the lateral part of the medial nucleus. Moreover, there were some degenerated nerve fibres in the mamillary capsule and in the supramamillary decussation. Since the last-mentioned type of degeneration was not found in the cases with lesions only in the field h 2, they probably came from the field h 3.

In four other cases (R 227, R 229, R 233, R 331) where there was more extensive hippocampal damage including the fields h 2 and h 3 (figures 15, 17 and 18) the same was found as in case R 286 besides some further degeneration.

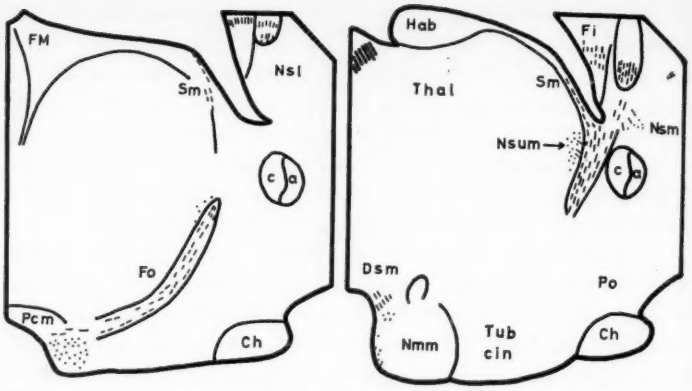

Figure 22: Two sagittal sections of the diencephalon of case R 286. The left one is about 1.5 mm lateral to the median plane and the right one is about 1 mm lateral to it, both on the side ipsilateral to the lesion. For abbreviations, see legend under fig. 13.

The field h 4:

This is rather small and the only cases (R 233 and R 239) where there was significant damage to this field included also injuries to other parts of Ammon's formation (figures 17 and 18). The hypothalamus of these rabbits did not contain any type of degeneration that could not be explained by the injury to the rest of the hippocampus.

The field h 5 and the fascia dentata:

The field h 5 is localized in the narrow hilus of the fascia dentata. With the technique used it was not possible to produce so small a lesion that it damaged this field exclusively. However, it has been possible to make a lesion in the fascia dentata from outside without any injury to the field h 5. The fimbrial fibres from this field leave via the hilus fasciae dentatae (Lorente de Nó 1934), and thus are not damaged by such a lesion.

In case R 229 (8d) there was damage to all the cortical layers of the lateral part of the fields h 2 and h 3 and the lesion extended into the ventricular segment of the fascia dentata (figure 18).

In the fornix system degeneration was found which terminated exactly as the fibres in case R 286. The amount of degenerated nerve fibres were also about the same in both cases and the lesions in the fields h 2 and h 3 were equally large as in case R 286.

In cases R 227 (7d) and R 331 (7d) the injuries were of the same type as in case R 229, but they also included lesions in the fimbria and the fornix longus respectively (figure 15). Not even in these cases could one find any degeneration that could not be explained by damage to other parts of Ammon's formation than the fascia dentata. Of course the results do not exclude connexions from the fascia dentata to the hypothalamus.

In the following four cases there was injury both to the fascia dentata and the field h 5 (figures 15–17 and 19).

R 225 (7d): The lesion went through Praecag and the radiatio corporis callosi and destroyed all cortical layers of the fields h 1, h 2, h 3?, h 5, the fascia dentata and the subiculum. Some of the penetrating fornix longus fibres from the cingulate area were also damaged. Extensive degeneration was found in the ipsilateral fornix with terminations in the medial septal nuclei, the nucleus supramedialis and perifornicalis and some degeneration also in the stria medullaris. In the mamillary body there was abundant terminal degeneration in the lateral nucleus and in the superior, posterior part of the medial nucleus. The mamillary capsule was heavily degenerated and also the supramamillary decussation (figure 23). In the latter the fibres cross to the contralateral side where they continue into the mesencephalon.

R 233 (6d): This lesion was more lateral and posterior than the former. It went via Str and involved all cortical layers of the fields h 2–h 5 and the fascia dentata. The degeneration in the fornix system was the same as in case R 225.

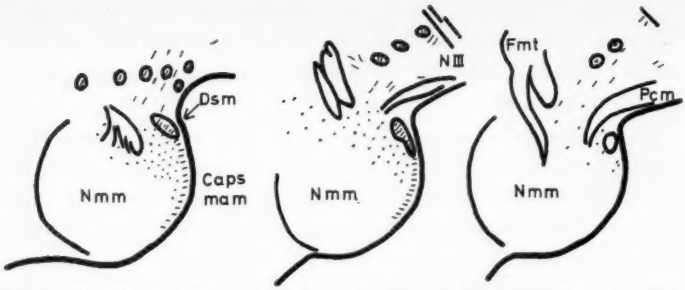

Figure 23: Three sagittal sections of the mamillary body of case R 225. The left section is at about the median plane and the two others about 0.3 and 0.6 mm lateral to it, on the side contralateral to the lesion. One sees clearly the mamillary capsule and the supramamillary decussation. The round rings above the mamillary body are the fascicles of the supramamillary decussation containing degenerated nerve fibres to the central grey on the side contralateral to the lesion. Posterior is to the right. For abbreviations, see legend under fig. 13.

R 245 (6d): This lesion was even more posterior. It involved the most caudal part of Ammon's formation with great damage to all cortical layers of the fascia dentata and the field h 5. There was also slight vascular involvement of the stratum lacunosum and moleculare of the field h 2. The lesion proceeded into the presubiculum and the entorhinal cortex. The degeneration was principally the same as in the two last cases. In case R 245, a peculiar but not seldom found anomaly of the fornix was seen. Part of the fornix fibres went in front of the anterior commissure and very closely around it. Having passed in front of it the fornix swung back to the main bundle again. Thus the commissure penetrated the fornix column.

R 358 (7d): This lesion was medial to that of case R 225. It went through Rsg β and the cingulum to the hippocampus where all layers of the fields h 2 and h 5 and the fascia dentata were destroyed. The lesion proceeded into the brain stem. In the fornix system the degeneration (figure 31) was about the same as in the three preceding cases but many other degenerated nerve fibres coming from the brain stem were also seen.

The subiculum:

There were five cases with significant lesions in the subiculum (figures 17–20).

R 239 (6d): The lesion lay in the inferior part of the medial aspect of the hemisphere and involved part of the fields h 4 and h 5 and the presubiculum on the surface, destroying all their layers, then went through the subiculum and ended in the area entorhinalis.

R 332 (7d): This lesion lay in the superior part of the medial surface and injured part of the subiculum and small parts of the adjacent presubiculum and the retrosplenial region. Then it proceeded into the habenula.

R 362 (4d): In this case there was distinct damage to the subiculum. However, it proceeded into the posterior part of the thalamus.

R 365 (6d): This lesion was somewhat anterior to the one in case R 332. It destroyed the subiculum and a small part of the retrosplenial region.

R 367 (6d): As well as the lesion in the subiculum there was also subsequent vascular damage to the presubiculum and retrospenial region. There was also a suspicion of a lesion on the mesencephalic surface.

The degeneration in the fornix system was of the same type in all cases. As an example, case R 365 will be described (figure 24). The degenerated nerve fibres came in the fornix longus. There were a few nerve fibres terminating in the medial septal region. The rest of the nerve fibres joined the column of the fornix medially. In this case there was the same type of variation in the position of the fornix as is described above in case R 245 (figure 29). The precommissural bundle was severely degenerated, in the postcommissural fornix there was only a little degeneration. From the postcommissural fornix degenerated nerve fibres entered the stria medullaris and some also terminated in the nucleus supramedialis. There were also some degenerated fibres in the nucleus perifornicalis. The descending column of the fornix was split up into many small bundles. Some of them entered the mamillary body. There was terminal degeneration in the medial mamillary nucleus, in its

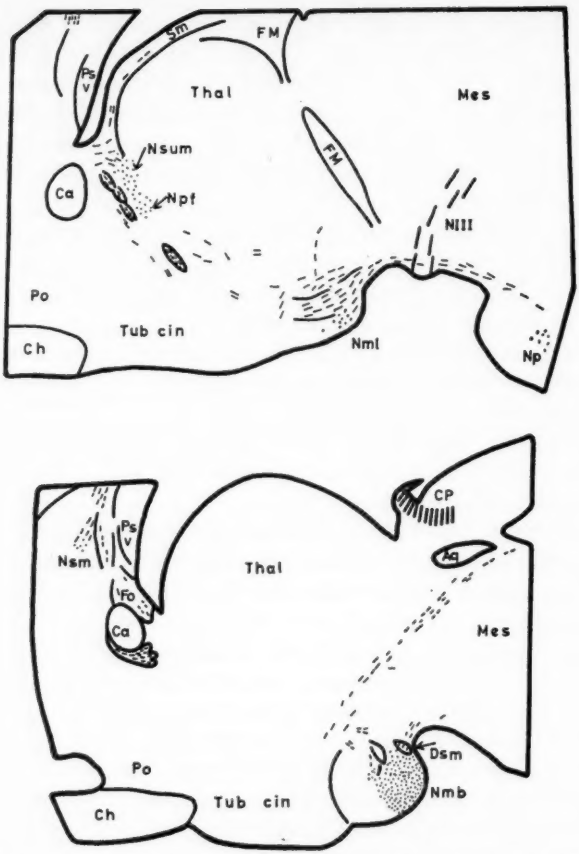

Figure 24: Two sagittal sections of the diencephalon and mesencephalon of case R 365. A is about 1 mm lateral to the median plane and B is about 0.5 lateral to it, both on the side ipsilateral to the lesion. One sees clearly that the fornix in this case goes partly anterior and around the anterior commissure, that it is split up into many fascicles in the tuber cinereum and that many degenerated nerve fibres go directly to the central grey and not via the supramamillary decussation. This is anomalous, compare fig. 22! The degenerated tract is also seen medial to the mamillary peduncle going in the base of the mesencephalon. For abbreviations, see legend under fig. 13.

ipsilateral posterior part corresponding to the nucleus basalis of M. Rose. Many nerve fibres proceeded into the mesencephalon. Some of them went in a basal tract just medial to the ipsilateral peduncle. It was possible to follow these nerve fibres into the pons where terminations were found in the nuclei pontis. Others were found in the mamillary capsule and the supramamillary decussation. From here they went to the contralateral part of the mesencephalon where they were found among the oculomotor nerve roots. Most of the mesencephalic fornix fibres, however, left the fornix in front of the mamillary body where distinct bundles went up to the periaqueductal grey. Here degenerated nerve fibres were found up to the posterior limit of the superior collicle. However, it was not possible to find the exact termination in the preparations.

In the other cases the fornix proceeded as usual and the mesencephalic fibres went via the supramamillary decussation to the central grey and the basal tract to the pons. In cases R 239 and R 362 there was no further degeneration in the hypothalamus, but in cases R 332 and R 367 the picture was somewhat complicated by nerve fibres from the brain stem lesion.

The taenia tecta:

The taenia tecta or induseum griseum is the rostral extension of the hippocampus. It contains only very few cells longitudinally arranged on the top of the corpus callosum and on the medial surface of the frontal lobe. There were at least four cases (R 172, R 227, R 299 and R 323) with injuries to the taenia tecta (figures 5, 9, 10 and 15) but because of the small number of cells destroyed here in each case no conclusions could be drawn.

Discussion:

During the last 80 years much has been done to study the fornix fibres to the hypothalamus and other parts of the brain stem both in normal animals and in animals with lesions to the hippocampus or to the fornix. However, most experimental

workers have produced very large lesions including other parts of the brain. No one has tried to confine the destructions to one of the many different cytoarchitectonic subdivisions of Ammon's formation and only very few (e. g. Cragg & Hamlyn 1959) have considered that other parts of the cortex would send fibres to the hypothalamus via the fornix. In the present work evidence has been presented that the regio retrosplenialis granularis does so and later fornix fibres from the presubiculum are described.

From the anatomical studies by von Koelliker (1894) and Cajal (1911) we know that fornix fibres from the subiculum go to the fornix longus. Daitz & Powell (1954) and Cragg & Hamlyn (1959) have obtained evidence that the fornix fibres from the area C A 1 (corresponding to h 1 + h 2) also do so. From the present study it is clear that the subicular fibres go via the fornix longus as the fibres from the regio retrosplenialis do. However, at least part of the fornix fibres from the field h 2 seem to pass via the alveus to the fimbria.

Septal fibres: It is well-known that part of the hippocampal fibres leave the fornix in the septal region. Besides terminating in the septal nuclei nerve fibres to the nucleus accumbens (Sprague & Meyer 1950) and to the nucleus of the diagonal band of Broca (Nauta 1956) have been described. According to Nauta, the precommissural nerve fibres also contribute to the medial forebrain bundle. In the present study special attention was paid only to the septum. Here degeneration in the medial septal nuclei was found in all cases with hippocampal or fornix lesions (figure 28). From the Glees stained preparations it was clear that many nerve fibres terminated with very fine plexiform arborizations around the perikaryon of the relatively large nerve cells (figure 43). No significant differences in the septal termination could be found in the different cases. In a few (R 229, R 233, R 358) with rather complicated lesions, some degenerated nerve fibres were followed in the direction of the nucleus accumbens and in the diagonal band of Broca, but the exact place of termination cannot be stated. This problem is beyond the scope of the present study.

Fibres to the thalamic region: Fornix fibres to the thalamus had already been described by Gudden (1881) and Ganser (1882). Cajal (1911) spoke of collaterals from the fornix to the anterior thalamic nucleus but Edinger & Wallenberg (1902) denied the existence of such fibres. After knife lesions in the fornix Sprague & Meyer (1950) were unable to find any fibres to the thalamus in the rabbit. Guillery (1956) and Nauta (1956), however, both using the Nauta & Gygax method on rats after large penetrating lesions to the hippocampus found a considerable number of degenerated nerve fibres in the thalamus.

In all the present cases with significant damage to some of the hippocampal regions, degenerated nerve fibres were found leaving the fornix just behind the anterior commissure (figure 30). These fibres were relatively thin. They are found in the anterior thalamic region just underneath the stria medullaris. In the preparations these fibres were not found to leave this region. They formed a plexiform layer around the cells of the nucleus supramedialis (according to the nomenclature of M. Rose 1935) and possibly also in the nucleus medialis anterior. Terminal degeneration was seen in the Glees stained preparations. The type of anterior thalamic degeneration was the same in all cases.

In many cases degenerated nerve fibres were also found in other parts of the thalamus. These fibres did not seem to have anything to do with the fornix fibre system.

In most cases degenerated nerve fibres were also visible in the stria medullaris on its way to the habenula.

Nerve fibres to the hypothalamus anterior to the mamillary body: In their Marchi study of the diencephalon of the rabbit after destruction of Ammon's formation, Edinger & Wallenberg (1902) found degeneration in the tuber cinereum in one animal. Simpson (1952) described degeneration in the ventromedial hypothalamic nucleus in monkeys with the Glees method. Nauta described (1956) degeneration in the medial hypothalamic region in the rat after lesions in the caudal hippocampus, but he was unable to confirm this result in the cat (1958).

Sprague & Meyer (1950) found no evidence of degenerated nerve fibres in this region of the rabbit.

In the present study no degeneration was seen in the tuber cinereum in the cases with hippocampal lesions. However, in the two cases with lesions to the stria terminalis (R 235, R 344) just the type of degeneration described by the previous authors was found. It is clearly evident from the studies of Nauta (1956) and Simpson and probably from the study of Edinger & Wallenberg that the nucleus amygdalae was damaged in their cases.

According to M. Rose (1935), Wahren (1957) and others, the fornix is surrounded by a concentric cell layer, the nucleus perifornicalis. Sprague & Meyer (1950) and Nauta (1956) described degenerated nerve fibres in the perifornical region. It is clearly evident in the present study that some nerve fibres leave the fornix during its passage through the hypothalamus and go a very short way. Most of them go dorsally and all of them seem to terminate in the nucleus perifornicalis (figure 32). Sometimes the column of the fornix is split up into many bundles slightly diverging into the hypothalamic region. However, the nerve fibre bundles seem to join again in front of the mamillary body.

The mamillary body: From all studies it is clear that the mamillary body in the rabbit can be divided into one lateral nucleus on each side with relatively large nerve cells and one medial, unpaired nucleus. The latter one is further subdivided by many authors into different parts. It seems to be convenient to speak of a nucleus ventralis (Wahren 1957) or nucleus basalis (M. Rose 1935) and a nucleus dorsalis (Wahren) or nucleus dispar (Rose), both unpaired. In addition, there is an intermediate region (nucleus intermedius, Rose) on each side where the fornix splits up. The posterior part of the medial nucleus is surrounded by a thin capsule with nerve fibres, radially arranged. This capsule is continuous with the supramamillary decussation.

Simpson (1952) and Daitz (1953) counted the fornix fibres

in the primates and showed that less than one-third of the subcallosal fornix fibres reached the mamillary body.

Probst (1901), Edinger & Wallenberg (1902) and Münzer & Wiener (1902) showed degeneration in the mamillary body after cortical destruction involving the hippocampus. Yamagata (1927, cf Allen 1944) traced fornix fibres to the lateral part of the mamillary body in Marchi preparations. After fornix lesions in dogs, Allen (1944) showed Marchi granulas in the external portion of the medial mamillary nucleus and a few in the lateral nucleus. Sprague & Meyer (1950) traced fornix fibres in the rabbit to the parts of the mamillary body corresponding to Rose's nucleus basalis and intermedius. Nauta (1956) and Guillery (1956) both working with the Nauta & Gygax method on rats and making transcortical lesions involving both the hippocampus and other parts of the brain described degeneration in much the same parts of the mamillary body as Sprague & Meyer. Lesions in the dorsal fornix of the rabbit (Cragg & Hamlyn 1959) gave fine pericellular degeneration in the lateral and caudal parts of the medial mamillary nucleus, mainly in its dorsal region.

In the present study, much the same type of degeneration as described by the authors mentioned was found in the cases with destruction in the whole of the hippocampus. The fornix fibres were split up in the intermediate region with some termination at this site. Part of the nerve fibres formed a plexiform layer with relatively large arborizations around the large nerve cells in the lateral nucleus. Most of the nerve fibres terminating in the mamillary body, however, went to the dorsal and posterior part of the medial nucleus mainly corresponding to the nucleus basalis of M. Rose. Abundant terminal degeneration was seen (figure 33). In the cases where the lesion was confined to the field h 2, however, all the degenerated nerve fibres were seen to go to the lateral mamillary nucleus.

Mesencephalic fibres: Edinger & Wallenberg (1902) traced fornix fibres in the supramamillary decussation to the mesencephalon. Cajal (1911) mentioned fornix collaterals at this site.

Sprague & Meyer (1950) stated that the descending fibres of the dorsal fornix project largely into the tegmentum. After lesions in the fornix they found fine degenerated fibres in the mamillary peduncle. Guillery (1956) saw degenerated fibres in the rostromedial part of the mamillary peduncle after lesions including the hippocampus in the rat. Nauta (1958) described hippocampal fibres to the rostral part of the central grey substance in the mesencephalon. After lesions in the dorsal fornix Cragg & Hamlyn (1959) were able to trace degenerated nerve fibres into the mamillary peduncle. These nerve fibres broke up into terminal arborizations around the neurons of the medial pontine nuclei.

The mamillary peduncle consists mainly of very thick nerve fibres. In a case (R 234) with a mesencephalic lesion in the region of the nucleus ruber almost all these thick fibres were degenerated (figure 37) and could mostly be followed to the lateral mamillary nucleus (figures 35 and 36), and some of them to the anterior part of the medial nucleus. However, a small tract just medial to the main peduncle containing very fine nerve fibres remained undegenerated. In the cases with lesions to the subiculum, the regio retrosplenialis granularis or to the fornix itself, the nerve fibres of just this mesencephalic tract were degenerated. It was possible to trace this tract further into the mesencephalon in some cases (with subicular lesions). Terminal degeneration was found in the nuclei pontis of the same side.

In all cases with lesions to the main fornix, the whole hippocampus, the fields h 3–h 5 or the subiculum, but not in the cases with the lesions confined to the field h 2, severe degeneration of the mamillary capsule (figure 34) and the supramamillary decussation (figure 38) was found. In some cases this degeneration could be followed crossing the midline and going in the direction of the aqueduct. In the central grey just under the aqueduct at about the level of the nucleus of Darkschewitsch they were lost. The exact place of termination was not found in the Glees stained preparations, but it seemed to be in the central grey.

CONCLUSIONS

In 19 rabbits the direct connexions from Ammon's formation to the hypothalamus were studied. All nerve fibres came via the fimbria or the dorsal fornix. In the hypothalamus these fibres terminated mainly in the mamillary body. A few were also seen in the nucleus perifornicalis but no pathway to the tuber cinereum was found. In the mamillary body there seemed to be a difference in the place of termination between the fibres coming from different parts of Ammon's formation. The fibres from the field h 2 ended mainly in the lateral nucleus, the fibres from the other parts mainly in the medial nucleus and here in its dorso-posterior part. The occurrence of nerve fibres from Ammon's formation to the septum, the thalamus and the mesencephalon has been mentioned.

IV. Bicortex

Cortical subdivisions:

Rose divided the bicortex or insula into nine different parts: the regio insularis prepyriformis (Prpy 1), the area preinsularis (Pi), the areas insularis agranularis anterior dorsalis (ai 1), anterior ventralis (ai 2), and posterior (ai 3) and lastly the areas insularis granularis anterior (i 1), intermedia (i 2), posterior (i 3) and extrema (i 4). Together they correspond to areas 13–16 according to Brodmann. It is relatively easy to identify the insular cortex owing to the presence of the claustrum. However, it is sometimes difficult to distinguish between the different subdivisions.

Present results:

In the present material there were eleven cases with significant damage to the insular cortex (figures 7, 8, 11 and 12). In six of them there were no degenerated nerve fibres in the hypothalamus.

R 204 (7d): As well as the definite lesion in the postcentral region, described above, there was very superficial damage to the insular cortex (i 1, ai 1 and ai 2).

R 237 (4d): This very large lesion started in the parietal cortex, went through the temporal and damaged the posterior part of the insular cortex (i 3 and i 4). All cortical layers and part of the claustrum were destroyed.

R 241 (4d): This lesion involved the superficial layers on both sides of the fissura rhinica anterior (i 3, ai 3 and Prpy 1) but not the claustrum.

R 249 (4d): The lesion, destroying all cortical layers, involved part of the tip of the insular cortex (Pi).

R 306 (10d): The lesion began in the postcentral cortex and involved a good deal of the middle insula (i 1, i 2, ai 1 and ai 2), where all cortical layers were destroyed in the middle part of the lesion (i 2 and ai 2).

R 320 (7d): A small lesion in the anterior part of the insular cortex (ai 1) involved the layers I–V. The staining picture was somewhat difficult to interpret in this case owing to artifacts of precipitated silver.

In the following five cases there was degeneration in the hypothalamic region.

R 242 (5d): This very large lesion was described above. In the insular cortex it involved the posterior part (i 3, i 4, ai 3 and Prpy 1). There was some degeneration in the hypothalamus, which is described later, and which was interpreted as due to damage to the prepyriform semicortex.

R 291 (4d): The lesion lay on the boundaries between the posterior insular cortex (i 4, ai 3 and Prpy 1) and the posterior prepyriform semicortex. In the lateral hypothalamus a few degenerated nerve fibres of the medial forebrain bundle type were seen.

R 305 (10d): The lesion involved all cortical layers but not the claustrum in the anterior region of the insula (ai 1, ai 2, i 1 and Prpy 1). There was a slight involvement of the prepyriform semicortex. In the preoptic region and lateral hypothalamus a few degenerated nerve fibres of the medial forebrain bundle type were seen.

R 315 (7d): The lesion began in Praecgr and went through the white matter (capsula interna and externa) to the insular cortex (ai 1, ai 2 and Prpy 1) and proceeded to the prepyriform semicortex beneath the olfactory tract. In the hypothalamus there was abundant degeneration of the medial forebrain bundle type, which is described later.

R 349 (6d): A very small lesion in the prepyriform insular cortex and also in the semicortex. Some possible degeneration was seen in the lateral hypothalamus.

It seems probable that the degeneration in the last five cases depended upon injury to the semicortex or subcortical

structures. Thus, no significant connexions from the bicortex to the hypothalamus were found. In the literature there have been no previous studies of this topic.

CONCLUSIONS

Eleven animals with lesions in the bicortex were used. No direct connexions to the hypothalamus could be found.

V. Schizocortex

A. REGIO PRESUBICULARIS

Cortical subdivisions:

This was divided by M. Rose into the area presubicularis dorsalis (Prsub 1), ventralis (Prsub 2) and parasubicularis (Parsub). The first two correspond to area 27 according to Brodmann and the last one to area 49. Rose & Woolsey named the area dorsalis the postsubicular area.

Present results:

It was rather difficult to make lesions in this part of the brain without injuring too much of the brain stem. Only in three cases was the lesion in the presubiculum large enough and the concomitant damage not too extensive (figures 9 and 10).

R 354 (5d): The lesion was confined to the presubiculum (Prsub 2) and the entorhinal cortex. Although not seen the electrode might have caused some damage on its way between the brain stem and the hemisphere. In the hypothalamus some degeneration was seen in the fornix going to the intermediate mamillary nucleus.

R 359 (7d): Even in this case the lesion lay in the same part of the presubiculum (Prsub 2) and went to the entorhinal cortex. There was some bleeding near the alveus where the electrode had passed. More degeneration was found in the fornix of this case going to the same part of the mamillary body as in the preceding case. A few fibres also entered the stria medullaris.

R 361 (6d): There was a vertical and rather small lesion starting in the subiculum and going through the whole of the presubiculum (Prsub 1) just into the entorhinal cortex. Even in this case degeneration was found in the fornix, the stria

medullaris and in the intermediate part of the mamillary body. A few fibres seemed to proceed into the mesencephalon.

In the following evidence is presented that none of the fornix fibres to the hypothalamus come from the entorhinal cortex. Thus, it seems possible that the presubiculum sends nerve fibres to the mamillary body. However, some of the degeneration may very well come from the hippocampus.

Previous investigations:

There have been no previous studies devoted to the presubicular connexions with the hypothalamus.

B. REGIO ENTORHINALIS

Cortical subdivisions:

M. Rose divided this region, or area 28 according to Brodmann, into nine different parts (e 1–9). However, it was very dificult to follow his subdivisions in all cases and to determine in which subarea the actual lesion was situated. The author instead tried to make the lesions together cover most of the region.

Presents results:

There were nine cases with significant damage to the regio entorhinalis (figures 9–12). In three of them there was no degeneration in the hypothalamus.

R 259 (7d): The lesion went through the temporal neocortex and extended into the lateral parts of the entorhinal cortex (e 1 and e 4).

R 356 (5d): A rather small lesion in the middle part of the entorhinal region (e 5 and e 7).

R 364 (6d): A relatively large lesion in the posterior part of the entorhinal cortex (e 8 and e 9). Concomitant damage to the mesencephalon produced degeneration in the dorsal supraoptic commissure.

In case R 242 there was a very large lesion mainly in the neocortex. This has already been described. It also damaged

the antero-lateral part of the entorhinal cortex (e 1 and e 2) and a part of the prepyriform semicortex. In the hypothalamus slight but typical degeneration was found in the medial forebrain bundle (see later).

In cases R 354 (damage to the middle part of the entorhinal cortex, e 5), R 359 (the middle part, e 5, e 6 and e 8) and R 361 (the posterior part, e 7 and e 8) as already described there was a lesion to the presubiculum and some degeneration in the fornix system. In case R 239 (injury to the posterior part of the entorhinal cortex, e 7 and e 8) there was also a lesion to the subiculum and some more degeneration in the fornix system. Finally, in case R 357 (5d) the lesion penetrated the brain stem, giving rise to considerable bleeding in the subarachnoidal space and also in the fimbria. It proceeded into the middle part of the entorhinal cortex. Here considerable degeneration was seen in the fornix.

In the present study no degeneration in the hypothalamus could be proved to come from the entorhinal cortex.

Previous investigations:

In a series of papers Adey and co-workers (1952 a, 1955, 1956 and 1958) studied the connexions of the entorhinal cortex in the monkey and in a marsupial phalanger. They used both degenerative methods (Glees, Marchi and Nauta) and the evoked potential technique. Histologically they found nerve bundles going from the entorhinal cortex via the capsula externa and the stria medullaris to the dorsal tegmentum but apparently no fibres terminating in the hypothalamus. Neurophysiological studies have further established the interrelationship with the mesencephalic region. Some response to entorhinal stimulation in the dorsal hypothalamus may perhaps imply fibres of passage in this region.

C. REGIO PERIRHINALIS

This is a very thin cortical area in the depth of the perirhinal sulcus. With the present method it was not possible to make

lesions confined exclusively to this area. In some of the animals (especially in case R 259) with lesions to the temporal neocortex and entorhinal cortex this area was also damaged. The results do not indicate any connexions with the hypothalamus.

CONCLUSIONS

Nine rabbits with lesions in the schizocortex were used. A pathway from the presubiculum to the mamillary body via the fornix was found. No direct connexions from the entorhinal or the perirhinal cortex to the hypothalamus seem to exist.

VI. Semicortex

A. REGIO PREPYRIFORMIS

Cortical subdivisions:

The lateral part of the prepyriform cortex (Prpy 1) has a claustrum. Owing to this fact and considerable phylogenetic data M. Rose (1931) considered it to be a part of the bicortex. The medial (Prpy 2) and intermediate (Prpy 3) parts of the prepyriform cortex go from the nucleus olfactorius anterior and cover the stria olfactoria lateralis. The regio prepyriformis corresponds to the anterior pyriform cortex or area 51 of other authors.

Present results:

In the present material there were three cases with extensive lesions in the prepyriform semicortex (figures 8 and 12). However, the close proximity to the medial forebrain bundle, the lateral olfactory stria and the anterior commissure made the results somewhat difficult to interpret.

R 242 (5d): This very large lesion has already been described under the neocortex. There was damage to the posterior part of the intermediate prepyriform cortex (Prpy 3) and the adjacent periamygdaloid cortex. The only degenerated nerve fibres in the hypothalamic region were some in the medial forebrain bundle. They passed through the nucleus of the diagonal band, the lateral preoptic region and the lateral hypothalamic region.

R 315 (7d): This lesion went through the frontal neocortex, the insular cortex and injured the anterior part of the prepyriform semicortex (Prpy 2) just beneath the lateral olfactory

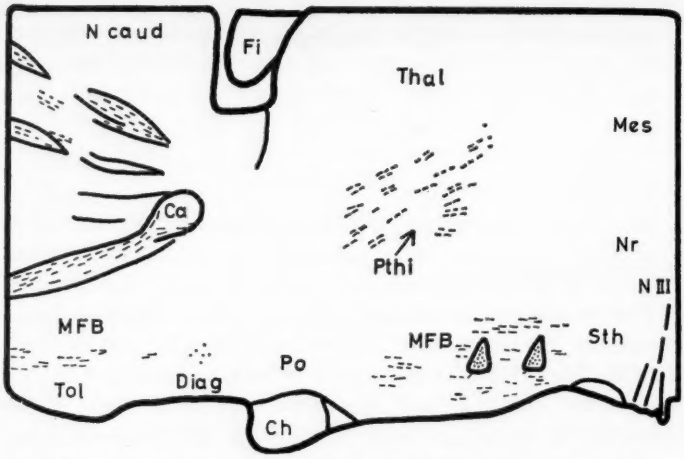

Figure 25: A sagittal section of the diencephalon and adjacent parts of the brain of case R 335 about 2 mm lateral to the median plane and ipsilateral to the lesion. Two pyramid-shaped nuclei are clearly seen in the posterior hypothalamus. They are described in the text and contain terminal degeneration from the medial forebrain bundle. For abbreviations, see legend under fig. 13.

tract. Extensive degeneration was seen in the medial forebrain bundle. There was terminal degeneration in the nucleus of the diagonal band. A large number of degenerated nerve fibres were found in the posterior hypothalamic region just lateral to the mamillary body. Some nerve fibres perhaps proceeded into the basal mesencephalon and the region of the nucleus subthalamicus but many ended in the posterior part of the hypothalamus. The details are discussed later.

R 335 (7d): Here there was a penetrating lesion going through the capsula externa and also a cortical lesion in the anterior prepyriform semicortex (Prpy 2) and the adjacent insular cortex. There was almost complete destruction of the lateral olfactory tract. The degeneration could be followed there in the preparations through the whole of the prepyriform semicortex to the olfactory tubercle and the nucleus amygdalae. Many other longitudinal tracts had degenerated and gave nerve

fibres to the nucleus accumbens and parts of the nucleus amygdalae. Both the lateral and the medial forebrain bundle contained many degenerated nerve fibres. Some proceeded into the diagonal band of Broca. However, some degenerated nerve fibres entered the lateral preoptic and hypothalamic areas (figure 25). There was distinct terminal degeneration in the posterolateral hypothalamic region.

Just lateral to the mamillary body there were two collections of nerve cells containing much terminal degeneration in cases R 315 and R 335 (figure 25). One of these collections was slightly anterior and the other slightly posterior to the lateral mamillary nucleus. The nerve cells were rather large and polygonal. The collections were shaped as pyramids with the top upwards (figure 39). The intercellular substance was very dense and the borders were very distinct. In the nerve-cell collections most of the nerve fibres were arranged vertically and the fibres from the medial forebrain bundle entered the collections horizontally, mostly from the bottom. There were both cytoarchitectonic and myeloarchitectonic reasons for considering these nerve-cell collections as separate nuclei. However, in the current literature about the rabbit diencephalon no description of these was found. They did not correspond to any nuclei in the works of for example Grünthal, Miura, M. Rose and Wahren.

According to Le Gros Clark & Meyer (1947) who studied the terminal connexions of the olfactory tract in the rabbit with the Glees method and Morin (1950) who used the Marchi method on guinea pigs no degeneration could be found in the medial forebrain bundle or the hypothalamus after resection of the olfactory bulb. Only in the last of the present cases was there significant damage to the lateral olfactory tract. Thus, it seemed improbable that the hypothalamic degeneration found should come from the olfactory bulb or tract. It has already been shown, that no direct connexions could be seen in the present material from the frontal neocortex or the bicortex to the hypothalamus. Thus, the medial forebrain bundle degeneration in these cases must have come from the prepiriform semicortex.

B. TUBERCULUM OLFACTORIUM

Present results:

It is still more difficult to place the lesions in the olfactory tubercle with stereotaxically placed electrodes without causing injury to other structures with possible connexions with the hypothalamus. Two cases are considered here (figure 11).

R 337 (7d): There was a rather distinct lesion in the anterior part of the olfactory tubercle. Very little subcortical damage was found. In the Nauta preparations dense degeneration was seen in the medial forebrain bundle. There was abundant terminal degeneration in the nucleus of the diagonal band and also in the lateral preoptic region. Many nerve fibres continued into the lateral hypothalamic area. The only sure terminal degeneration was found in both the nuclei described above lateral to the mamillary body.

R 350 (6d): As well as a lesion of the posterior part of the olfactory tubercle, there was a relatively large destruction in the subcortical region affecting both the anterior commissure,

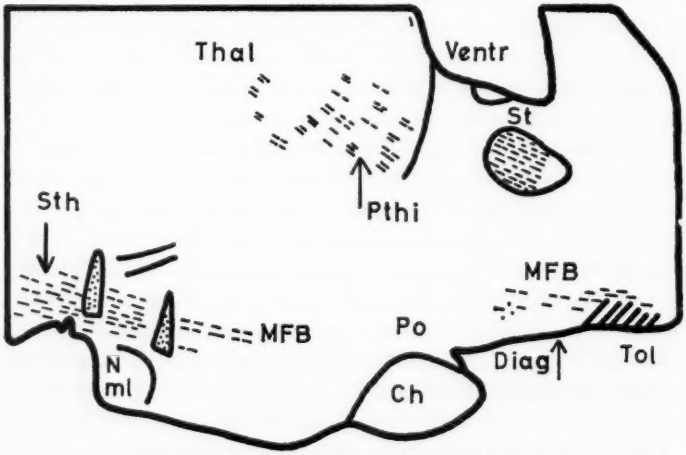

Figure 26: A sagittal section of the diencephalon and adjacent parts of the brain of case R 350 about 2 mm lateral to the median plane and ipsilateral to the lesion. The oblique hatched area indicates the medial part of the lesion in Tol. For abbreviations, see legend under fig. 13.

the nucleus accumbens and the nucleus of the diagonal band. Degenerated nerve fibres were found in the capsula interna, in the anterior commissure, in the inferior thalamic peduncle and in the olfacto-habenular tract according to Loo (1931). The nucleus of the diagonal band contained many degenerated nerve fibres. In the medial forebrain bundle many nerve fibres were seen going through the lateral preoptic and hypothalamic regions. There was considerable terminal degeneration in the posterior hypothalamic region especially in the two nuclei lateral to the mamillary body (figure 26). In the rest of the hypothalamus no degeneration was found.

Previous investigations:

There have not been any previous experimental studies about the connexions from the olfactory tubercle to the hypothalamus. However, Gurdjian (1927) mentioned a tractus tuberculo-hypothalamicus in rats and Loo (1931) a tractus olfacto-hypothalamicus in the opossum. These tracts both seem to connect the olfactory tubercle in part at least with the hypothalamus and are also probably parts of the medial forebrain bundle. From case R 350 it was not possible to state that the above described degenerated nerve fibres in the hypothalamus came from the olfactory tubercle, but in case R 337 this was apparently so.

C. REGIO DIAGONALIS AND D. SEPTUM PELLUCIDUM

These structures were considered by M. Rose and many others as parts of the cerebral cortex. For the discussion of this topic from a phylogenic and ontogenic point of view the reader is referred to the papers of Johnston (1923), Kappers, Huber & Crosby (1936) and Thomalske, Klingler & Woringer (1957). The diagonal and the septal areas are topographically lying very close to the hypothalamus and many nerve fibre bundles pass these structures. Therefore, it does not seem possible to investigate the connexions from them to the hypothalamus experimentally without making a thorough study of

all fibre systems in this region. This is beyond the scope of the present paper and work is still in progress. Hence, no available data will be given here.

E. REGIO PERIAMYGDALARIS

Subdivisions:

The amygdaloid complex has been described in rabbits by Johnston (1923) and Young (1936), in rats by Gurdjian (1928) and Brodal (1947a) and in the cat by Fox (1940). Rose's regio periamygdalaris seems to correspond to the nucleus corticalis and partly to the nucleus medialis of these authors. Others (Gloor 1955) do not seem to include the periamygdaloid cortex in the amygdaloid nucleus. Rose further divided the cortical area of the rabbit into six parts.

Present results:

In the present study there was only one case where the lesion was confined to the cortical part of the amygdaloid complex. In this case (R 292, 6d) the lesion was localized to the antero-lateral part of the cortical nucleus and no degenerated nerve fibres were found in the hypothalamus.

Case R 242 (5d) also had a lesion in the prepyriform semi-cortex. Here was found the above described typical medial forebrain bundle degeneration.

The next case, R 338 (7d), as well as a small lesion in the lateral part of the cortical nucleus had damage to the lateral and central nuclei and to the anterior commissure fibres in this region. In the hypothalamus there was considerable degeneration in the medial forebrain bundle (figure 40) with terminal arborizations in the nucleus of the diagonal band and in the posterior hypothalamic region, mostly in the two earlier described nuclei (figures 41, 42, 44 and 45).

R 342 (7d) showed about the same as the preceding animal.

In case R 348 (5d) with very extensive destruction both in the cortical, medial and central nuclei of the amygdala there was also direct hypothalamic damage.

In none of these five cases (R 242, R 292, R 338, R 342 and R 348) which taken together had injuries in the whole of the cortical nucleus (figures 11 and 12) was there any degeneration in the hypothalamus coming via the stria terminalis. In the cases where considerable degeneration in the hypothalamic part of the stria going just in front of the anterior commissure and radiating into the medial hypothalamic region with terminations mostly to the ventromedial nucleus was found, the damage was not to the cortical nucleus of the amygdala but to other parts including direct injury to the stria. Thus, no evidence of a component from the periamygdaloid cortex to the hypothalamic part of the stria terminalis was found.

Whether the medial forebrain bundle fibres described in cases R 242, R 338 and R 342 came from the periamygdaloid cortex or from other structures could not be determined on the basis of the present investigations, but the negative findings in case R 292 are against the first assumption.

Previous investigations:

Fox (1943) using the Marchi technique on cats with lesions in the amygdaloid area concluded that the larger number of the stria terminalis fibres take origin in the basal nucleus. Adey & Meyer (1952a) working on monkeys stated that stria terminalis "appears to be more closely related to the posterior basolateral parts of the amygdaloid complex than to the corticomedial group".

There has not previously been any experimental work concerning the connexions of the periamygdaloid cortex. Gurdjian (1928) working on rats and Fox (1940) working on cats briefly mentioned fibres from the cortical nucleus to the stria. This has, however, many components going to other structures than the hypothalamus (Johnston 1923).

Gloor (1955) found short latency responses in the hypothalamus after stimulation of the cortico-medial subdivision of the amygdaloid complex in the cat. But, as is clearly seen from his pictures, he did not include the periamygdaloid cortex (called by him "cortex piriformis") in the amygdaloid complex, and his electrodes were not placed here.

CONCLUSIONS

Nerve fibres to the hypothalamus have been found both from the regio prepyriformis and from the tuberculum olfactorium. These nerve fibres constituted a part of the medial forebrain bundle which passed through the whole of the lateral hypothalamus. Terminal degeneration was found only in the posterior part of the lateral hypothalamus, mainly in two nuclei just anterior and posterior to the mamillary body. The degeneration found seemed to be strictly ipsilateral. From the periamygdaloid cortex no direct connexions to the hypothalamus were seen.

General Discussion

The Staining Methods

The Nauta & Gygax (1954) method have given a fairly good staining picture when applied to the rabbit diencephalon. The degenerating axons were easily followed and there were not very many artifacts of precipitated silver. However, as pointed out by Evans & Hamlyn (1956), it was necessary to use controls. When interpreting the results the author had very much help from the control cases with lesions in the tracts themselves near the hypothalamus.

The Nauta & Gygax method stains much of the terminal arborizations in the hypothalamus. It is easy to understand that a tract terminates in a nucleus if it is seen that the previously parallel fibres split up forming a network around the cells. However, no certainly degenerated boutons were observed with this method.

From the beginning, the Glees method failed completely in the hypothalamus on the section where other parts of the brain stem were present which gave good staining pictures. Heavy overstaining in the diencephalon was avoided by dilution of the ammonia silver solution. However, passing fibres were very difficult to follow and the author used the Glees method only for studying the boutons or the terminals of the pericellular plexus.

The Results

It is beyond the scope of this study to discuss the immense literature about cortical vegetative regulation and to consider the relations between anatomical and physiological results. However, the following considerations seem justified.

From the present study it is clear that in the rabbit the cortical pathways to the hypothalamus come via the medial forebrain bundle or the fornix. It is also obvious that these tracts in the hypothalamus terminate mainly in the posterior region or in the mamillary body. About the function of the mamillary body very little is known. It has been customary to include the mamillary body as well as the hippocampus and the holocortex quinquestratificatus in the "visceral brain" of MacLean (1954 and 1955). However, in a recent review Kaada (1960) pointed out that there is a considerable lack of evidence of a "visceral" function of the hippocampus-fornix-mamillary system. He further stated that there are no indications of a vegetative function of the posterior part of the cingulate gyrus (corresponding to part of the regio retrosplenialis granularis in the rabbit).

That the postero-lateral part of the hypothalamus takes part in autonomic regulation is strongly evident from many studies, for example those of Hess (reviewed 1956). The function of the cortical areas sending nerve fibres to this part of the hypothalamus—the olfactory tubercle and the prepyriform cortex—is less well-known. They receive direct fibres from the olfactory bulb (for literature see Brodal 1947 b and Pribram & Kruger 1954) and the medial forebrain bundle is primarily an olfactory structure (Brodal). Whether the fibres reaching the hypothalamus have anything to do with olfaction is not known. However, it seems to be clear that the prepyriform cortex and the olfactory tubercle are involved in autonomic regulation (see e. g. Kaada 1951 and 1960).

In the present study no nerve fibres were found from the cortex to the tuber cinereum. In the beginning this may seem strange. But as we know, this part of the hypothalamus is mainly concerned in the regulation of the endocrine system (ref. see Harris 1955, Lundberg 1955 and 1956). In addition it has a very unusual histological structure (see e. g. Spatz, Diepen & Gaupp 1948, Bargmann 1954, Lundberg 1957). From many points of the cerebral cortex electrical stimulation gives rise to vegetative responses such as effects on gastric motility and blood pressure (see e. g. Kaada 1951). However, endocrine

effects, such as ovulation in the rabbit or oxytocin secretion (Koikegami et al 1954, Shealy & Peele 1957) have only been reported after stimulation of the amygdaloid region, which has, in fact, a direct connexion to the tuber cinereum—the stria terminalis.

The nerve tracts coming from the cortex to the hypothalamus seemed all to be ipsilateral. No obviously crossed fibres were found in the hypothalamus, except those in the supramamillary decussation. However, the medial mamillary nucleus is an unpaired structure. It is sometimes difficult to determine the side in a structure very close to the median plane if the preparation is sectioned sagittally. It was clearly seen in the preparations that the main degeneration in the medial mamillary nucleus was in its ipsilateral half. However, some degeneration was also found in the contralateral half.

Another point of interest is, that in the rabbit at least, relatively so few cortical regions send nerve fibres directly to the hypothalamus, that most of them come from the "oldest" part of the cortex, and none come from the neocortex. On the other hand, the thalamus receives nerve fibres from many parts of the cortex (ref. see Kuhlenbeck 1954). It is apparent that the cortico-thalamic fibres come mainly from the neocortex and from those parts of the cortex that do not send any tracts to the hypothalamus. Phylogenically the (dorsal) thalamus develops much more than the hypothalamus (ref. see Kappers, Huber & Crosby 1936, Kuhlenbeck 1954). The hypothalamus is in many respects one of the most primitive parts of the brain. Hence, it is not surprising that the "older" parts of the cortex sends nerve fibres to the "older" part of the diencephalon and that the neocortex' fibres go to the more developed thalamus.

Brodal (1948) pointed out that the attempts to establish direct, cortico-hypothalamic fibres have given meagre results with the exception of the fornix. He also assumed that the other cortical areas may affect the hypothalamus indirectly, "probable first and foremost via the thalamus". Kuhlenbeck & Haymaker (1949) stated that "most of the neocortical impulses which reach the hypothalamus travel by way of fibers which

synapse in rostral and ventral thalamic nuclei whose axis cylinders reach the hypothalamus via the periventricular system and the inferior thalamic peduncle".

Other types of indirect (trans-synaptic) connexions from the cortex to the hypothalamus may be assumed. Cajal (1893 and 1911) and Lorente de Nó (1934) and many others, have studied extensively the nerve paths from the area entorhinalis to the hippocampus. By this route the hypothalamus may be influenced.

After destruction in the anterior cingulate area (= part of the area infraradiata of M. Rose) of the rabbit and monkey, Adey (1951) and Adey & Meyer (1952 b) traced degenerated nerve fibres in the cingulum both to the posterior cingulate area (= part of the regio retrosplenialis granularis) and to the presubiculum. In the present work direct hypothalamic connexions have been shown from the latter two regions. Here is another route by which the cortex may act on the hypothalamus.

Finally a few words about the validity of the present findings in the rabbit for other animals including man. It has already been pointed out that some parts of the cortex, especially the neocortex, have undergone a tremendous evolution in higher animals (Kappers, Huber & Crosby 1936). Woolsey (1958) stated that in the rabbit the sensory-motor cortex takes most of the neocortex and very little place is left for association cortex. But even in the cat such a cortex is beginning to develop. This fact is especially pronounced in the frontal cortex. In the review on page 21 of the previous investigations on the corticofugal connexions of the frontal cortex, some findings, possibly controversial, of fibres to the hypothalamus in the higher animals have been mentioned. In the present study of the rabbit none were found. It is clearly possible that when a cortical region develops nerve connexions also develop to different parts of the brain stem.

The older parts of the cortex seem to remain more alike qualitatively in the higher animals. Quantitatively, however, progressive development is conspicuous in some parts of the older cortex, e. g. the hippocampus. Thus, one would expect

that the tracts from the older parts of the cortex to the hypothalamus are principally the same in the different animals, but more abundant in man and the monkey than in the rabbit. This opinion is supported by the quantitative studies of the fornix system by Daitz (1953) and Powell et al (1957) in these animals.

Summary

1. With a stereotaxic technique or with a knife and sucker, lesions have been made in the cerebral cortex of rabbits. The animals were killed between 4 and 17 days after the operation. The occurrence of degenerated nerve fibres in the hypothalamus were studied by the method of Nauta & Gygax (1954) and that of Glees. The results were based on 111 cases (including the controls).
2. Degenerated nerve fibres were found in the fornix after lesions in the formatio Ammonis, the regio retrosplenialis granularis and the regio presubicularis. In these cases terminal degeneration in the hypothalamus was found in the nucleus perifornicalis and in the mamillary body. After lesions in the field h 2 of the hippocampus terminal degeneration was found in the lateral mamillary nucleus, but after lesions in other parts of Ammon's formation mainly in the medial nucleus. Connexions from the mentioned regions to other parts of the brain stem are briefly described.
3. After lesions to the regio prepyriformis and to the tuberculum olfactorium degenerated nerve fibres were observed in the medial forebrain bundle to the posterior part of the hypothalamus. Here the terminal degeneration was found mainly in two previously undescribed nuclei lateral to the mamillary body.
4. After lesions to the neocortex, the regio infraradiata, the bicortex or to the regio entorhinalis no degeneration was found in the hypothalamus.

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Plates

PLATE I

Figure 27: The lesion in case R 365. To the left one sees the normal cortex, to the right a complete destruction and between a reactive zone with glial and mesenchymal-cell proliferation. The animal was killed 6 days after the operation. Gomori stain. 50×.

Figure 28: Degenerated, very thin nerve fibres leaving the column of the fornix superior to the anterior commissure and going into the septal region. Case R 358. Nauta & Gygax stain. 800×.

Figure 29: Here one sees the anomalous path taken by part of the fornix fibres around the anterior commissure. This part of the fornix is heavy degenerated. The other part going posterior to the commissure contains very few degenerated nerve fibres and thus in this magnification is coloured as the non-degenerated commissure. Case R 365. Nauta & Gygax stain. 20×.

Figure 30: Degenerated nerve fibres leaving the fornix (to the left) and entering the nucleus supramedialis thalami. Case R 227. Nauta & Gygax stain. 800×.

PLATE II

Figure 31: Degenerated nerve fibres in the fornix. Case R 358. Nauta & Gygax stain. 800×

Figure 32: A few degenerated nerve fibres, mostly preterminals, in the nucleus perifornicalis. Case R 227. Nauta & Gygax stain. 800×.

Figure 33: Extensive degeneration in the medial mamillary nucleus. Case R 227. Nauta & Gygax stain. 800×.

Figure 34: The lower part of the picture is the glia layer on the outer surface of the mamillary body underneath the pia. The middle part is the mamillary capsule containing nerve fibres from the fornix, entering the basal mamillary nucleus uppermost in the picture. Case R 227. Nauta & Gygax stain. 800×.

PLATE III

Figure 35: The lateral mamillary nucleus in case R 234 on the side ipsilateral to the lesion of the mamillary peduncle. One sees a very heavy

degeneration taking most of the nerve fibres in this region. Nauta & Gygax stain. 200 ×.

Figure 36: A detailed picture of one cell from the preceding picture. An extensive degeneration is seen around the cell. Many degenerated nerve fibres are preterminal, others seem to terminate on the perikaryon. Nauta & Gygax stain. 1300 ×.

Figure 37: Degenerated, thick nerve fibres in the mamillary peduncle of case R 234. Nauta & Gygax stain. 800 ×.

Figure 38: Degenerated nerve fibres in the supramamillary decussation. Case R 358. Nauta & Gygax stain. 800 ×.

PLATE IV

Figure 39: One of the pyramid-shaped cell collections in the posterior hypothalamus lateral to the mamillary body (case R 338). Most of the nerve fibres seen are non-degenerated. The horizontal tract is part of the medial forebrain bundle. Glees stain. 50 ×.

Figure 40: A few degenerated nerve fibres passing the lateral hypothalamic area as a part of the medial forebrain bundle. Case R 338. Nauta & Gygax stain. 800 ×.

Figure 41: Preterminal degeneration in the posterior hypothalamic area of case R 338. Nauta & Gygax stain. 800 ×.

Figure 42: Preterminal degeneration in one of the pyramid-shaped nuclei in the posterior hypothalamus lateral to the mamillary body. Case R 338. Nauta & Gygax stain. 800 ×.

Figure 43: One cell in the medial septal region. To the right a very thin degenerated terminal arborization is seen. Case R 358. Glees stain. 1600 ×.

Figure 44: The upper arrow indicates a degenerated bouton and the lower one indicates its preterminal fibre. This picture and the following one is from one of the two pyramid-shaped nuclei in the posterior part of the hypothalamus lateral to the mamillary body. Case R 338. Glees stain. 1600 ×.

Figure 45: The arrow indicates a degenerated bouton, its preterminal fibre is downwards. Glees stain. 1600 ×.

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Plate I

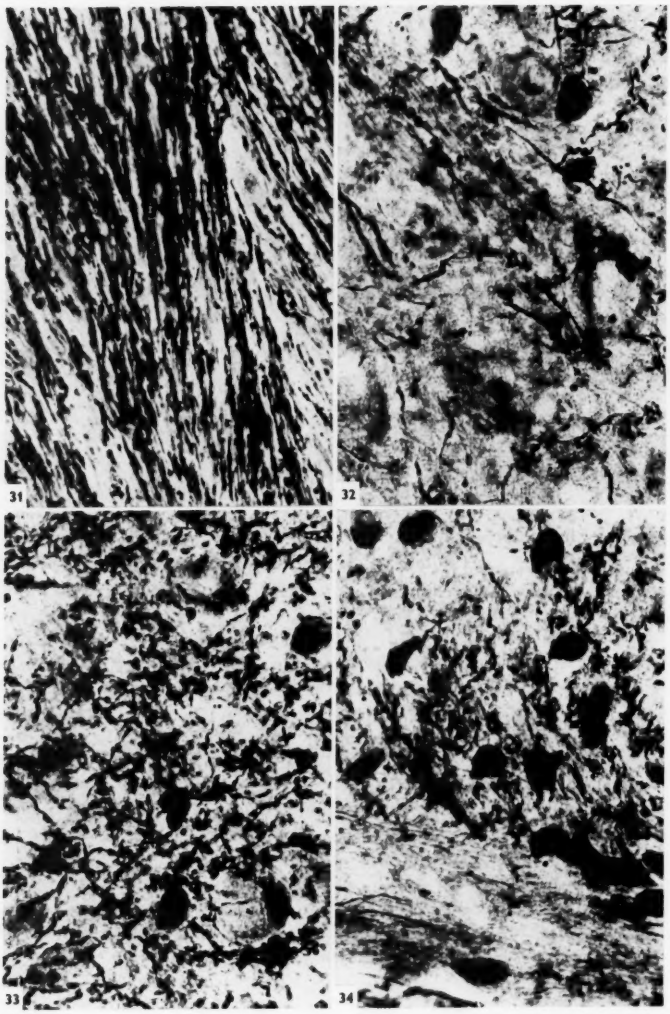


Plate II

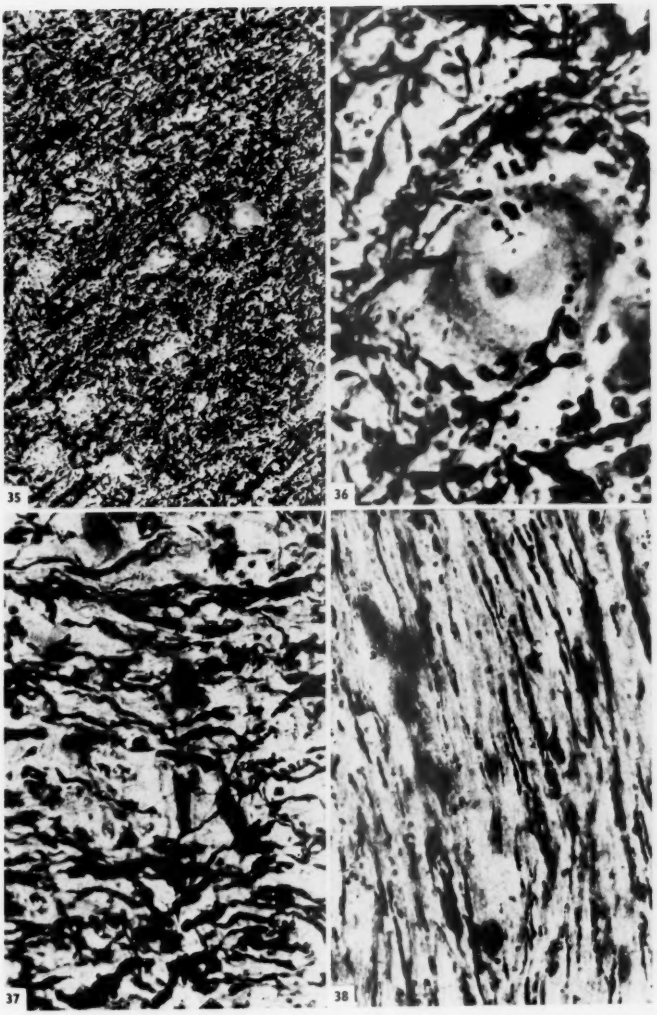
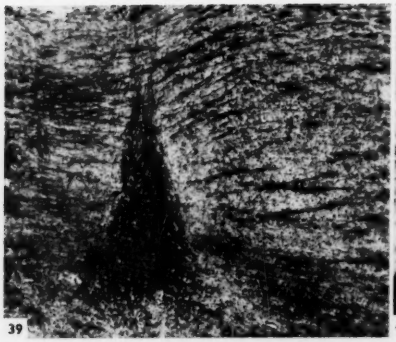
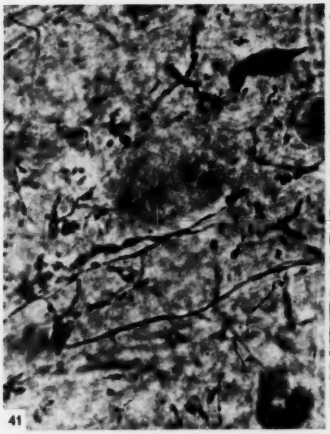
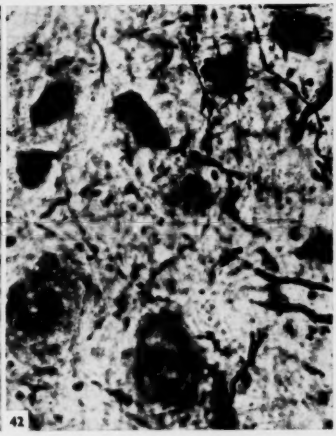


Plate III







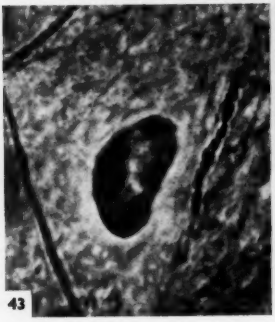


Plate IV